

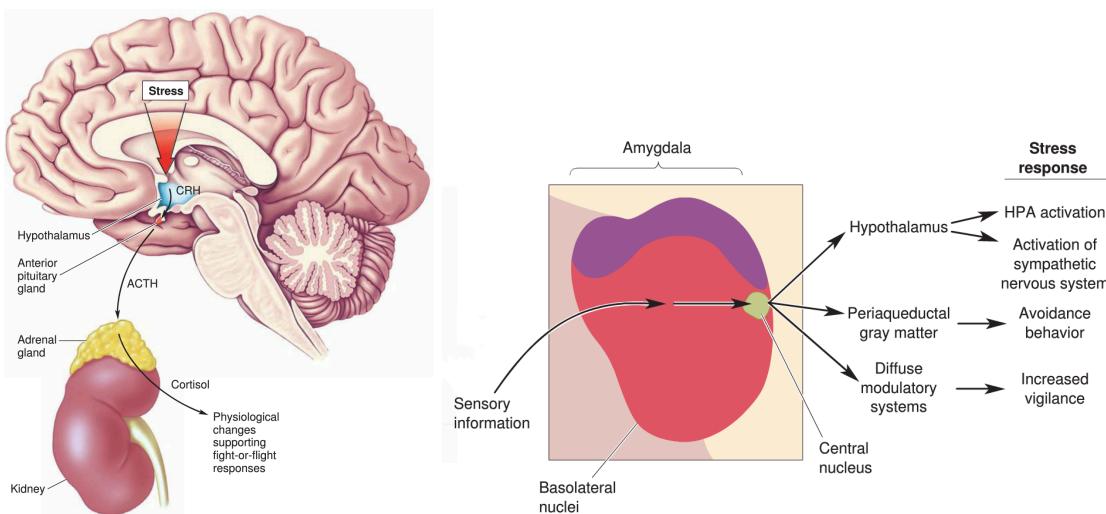
Lecture 40. Psychiatric Disorders

Prof. Melissa Warden

Pre-Lecture Preparation

Watch Video 40-1: The stress response

Understand these figures:



Required Reading

Be able to explain the following figures from Bear et al.: p.759, Fig. 22.3; p.760, Fig. 22.5; p.761, Figs. 22.6-7; p.766, Fig. 22.9; p.769, Fig. 22.11; p.772, Box 22.3; p.776, Fig. 22.16; p.777, Fig. 22.18

Optional Reading

Deep brain stimulation for treatment-resistant depression. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH.

Learning Objectives

1. To understand the role of the HPA axis and the amygdala in mood disorders.
2. To learn the major clinical signs of mood disorders and schizophrenia, and to be able to describe the biological signs of these illnesses in the brain.
3. To understand the interaction between genetic predisposition and environmental risk factors that may trigger schizophrenia in a genetically vulnerable population.
4. To learn the major actions of the primary drug treatments for each disorder.

Lecture Outline

Understanding the neural basis of psychiatric disorders is important for two reasons. First, we wish to alleviate suffering and come up with new treatments for disease. Second, neural dysfunction often gives us unique insights into the mechanisms of normal neural function. Today, we will discuss two diseases that affect normal human cognitive function, for which we do not know the underlying mechanism, but for which we do have reasonably good treatments: schizophrenia and mood disorders.

1. The stress response
 - a. Hypothalamic-pituitary-adrenal (HPA) axis activation
 - b. Amygdala
2. Mood Disorders
 - a. Definitions of the major mood disorders
 - b. Nature vs. nurture. Genetic vulnerability and environmental stress
 - c. Neural circuits involved in mood disorders
 - i. Neuromodulators
 - ii. Frontal cortex
 - d. Drug treatments
 - i. Selective serotonin reuptake inhibitors
 - ii. Ketamine
 - e. Non-drug treatments
 - i. Electroconvulsive therapy
 - ii. Deep brain stimulation
3. Schizophrenia
 - a. Clinical description of schizophrenia
 - i. Positive and negative symptoms
 - b. Changes in brain structure and function of schizophrenics
 - i. Structural abnormalities
 - ii. Changes in connectivity
 - iii. Hypofrontality
 - c. Genetic predisposition
 - d. Environmental risk factors for schizophrenia
 - e. Treatment of schizophrenia
 - i. Dopamine D2 receptor antagonists block positive but not negative symptoms
 - ii. But no data suggesting strong changes in dopamine function in schizophrenic brain – drugs may evoke homeostatic response.

Study Questions

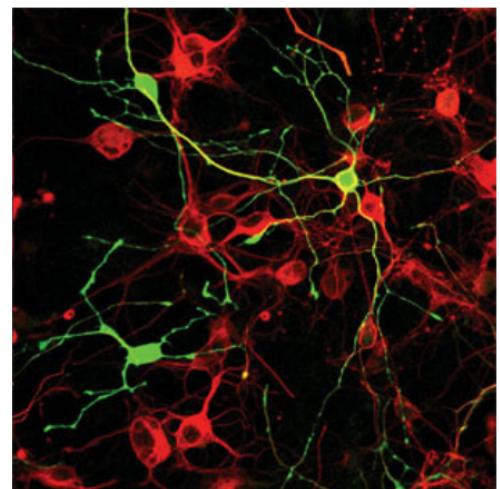
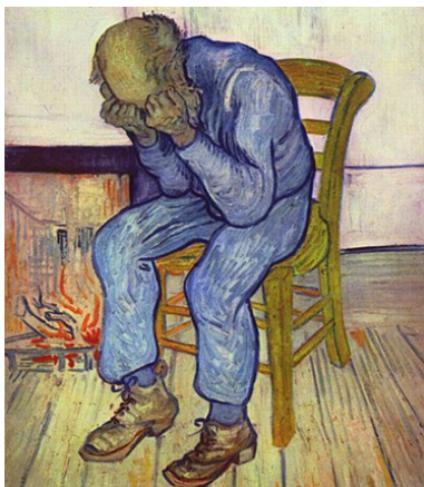
1. Discuss why the very slow onset of action of antidepressant drugs makes it difficult to understand how they are actually helping with the clinical manifestations of the disease.
2. If these diseases show such a strong genetic predisposition, what kinds of actions can the environment activate to contribute to the cause of mental illness?

NEUROBIOLOGY AND BEHAVIOR II: INTRODUCTION TO NEUROSCIENCE

BioNB 2220

Lecture 40: Psychiatric Disease
May 3, 2019

Melissa R. Warden, PhD



The diathesis-stress hypothesis

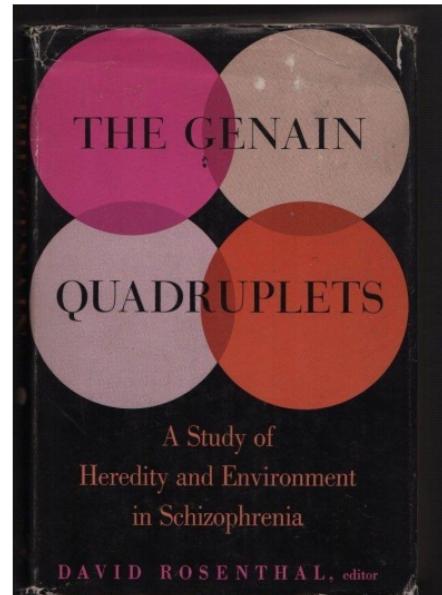
Diathesis = predisposition.

Stress + individual predisposing characteristics = an episode of mental illness

The stress-vulnerability hypothesis is a similar idea.

Predisposing factors:

- genes
- trauma at birth
- early life stressors (childhood abuse and/or neglect)



Journal of Abnormal Psychology
1977, Vol. 86, No. 2, 103-126

Vulnerability—A New View of Schizophrenia

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Columbia University and New York State
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Research Unit

Bonnie Spring
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Psychiatric Institute, Biometrics
Research Unit

Although descriptive and etiological approaches to psychopathology have made notable advances, they seem to have reached a plateau. After reviewing the six approaches to etiology that now preempt the field—ecological, developmental, learning, genetic, internal environment, and neurophysiological models—a second-order model, vulnerability, is proposed as the common denominator, and methods for finding markers of vulnerability are suggested in the hope of revitalizing the field. It is assumed that exogenous and/or endogenous challengers elicit a crisis in all humans, but depending on the intensity of the elicited stress and the threshold for tolerating it, that is, one's vulnerability, the crisis will either be contained homeostatically or lead to an episode of disorder. Vulnerability and episode stand in a trait-state relation, and markers for each must be provided to distinguish between them.

Schizophrenia: a thought disorder

Positive signs:

- Disturbed form and content of thought
- Bizarre delusions (paranoia, delusions of grandeur)
- True hallucinations (usually auditory)

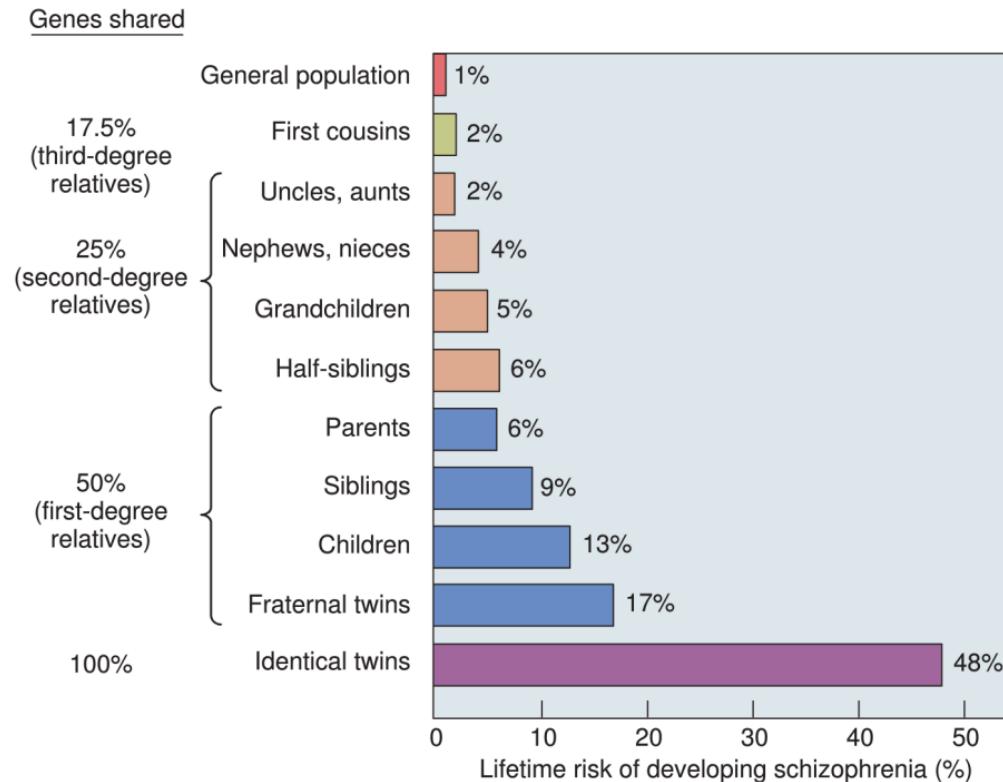
Negative signs:

- Inappropriate affect and emotional flattening
- Social withdrawal
- Lack of motivation

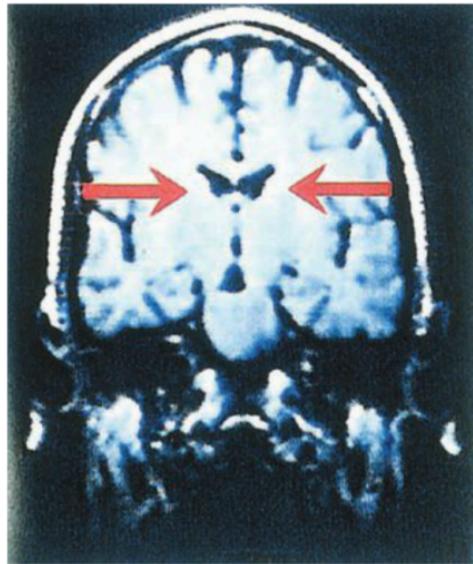
Cognitive deficits:

- Low IQ (1 SD below normal)
- Deficits in working memory and episodic memory
- Deficits in goal representation

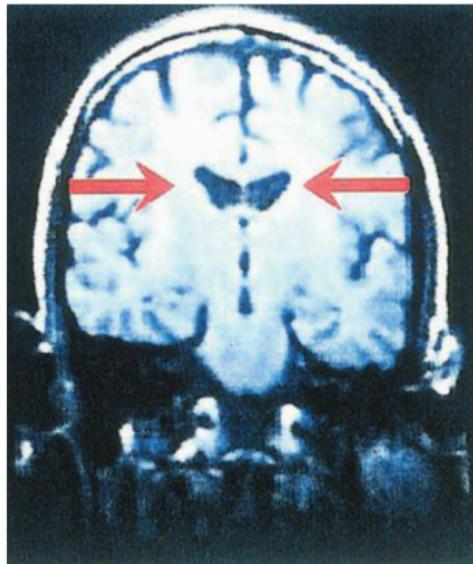
Genetic predisposition for schizophrenia



Physical brain differences in schizophrenia



Normal twin



Schizophrenic twin

The schizophrenic twin has enlarged lateral ventricles, indicating a loss of brain tissue
Life history, experiences may cause brain differences, leading to vulnerability

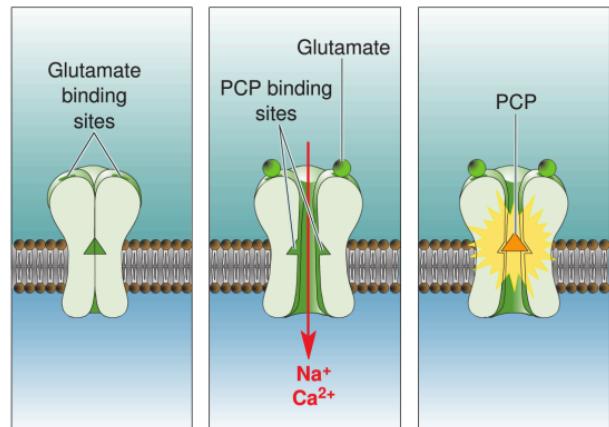
Street drugs suggest possible neural basis

Phencyclidine (PCP, angel dust) and Ketamine (special K)

- Originally introduced as anesthetics
- Sub-anesthetic dose mimics positive and negative symptoms of schizophrenia
 - Includes hallucinations and paranoia
- Both drugs are NMDA receptor antagonists

Glutamate hypothesis of schizophrenia

- Somewhat vague – doesn't mean we understand how circuit operation has changed
- But it is an organizing idea that is inspiring current research



Mood disorders

Defining symptom is low mood

Examples of mood disorders:

- Major depression (unipolar)
- Dysthymia (low grade, long-lasting depression)
- Seasonal affective disorder
- Bipolar disorder (cycling between depression and mania)

Highly comorbid with anxiety disorders

Emotion and mood

Emotions are transient reactions to external or internal stimuli

- Coordinated adaptive response to important events
- Associated with physiological and behavioral changes

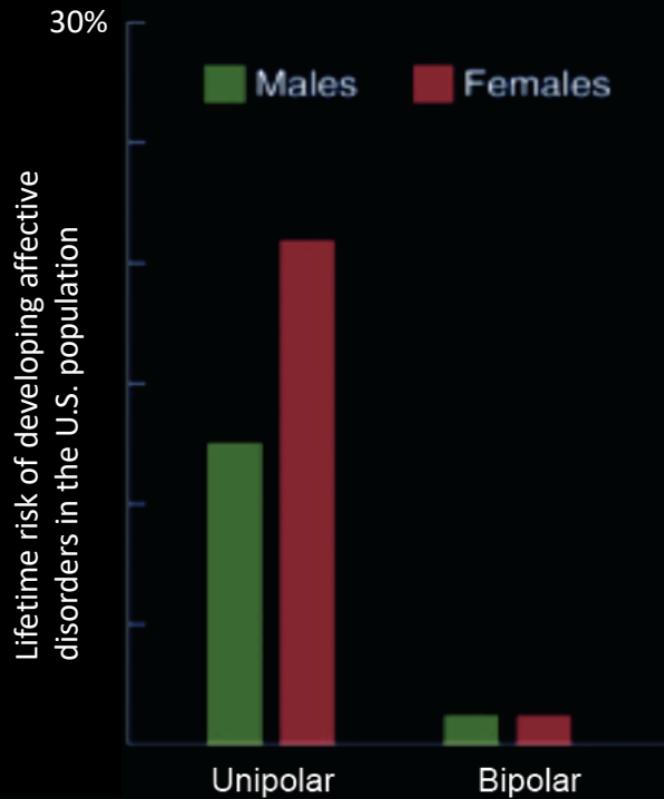
Mood is the predominant emotional state over time

Depression

- Depressed or irritable mood
- Decreased interest in pleasurable activities and ability to experience pleasure
- Significant weight gain or loss (>5% change in a month)
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or suicide

Presence of most of these symptoms for at least 2 weeks

Depression: Occurrence & Gender



- Unipolar depression can occur at any age, and affects ~5% of the population at any one time.
- Twice as common in women than men (equally common for bipolar depression).
- However, this gender difference only emerges after puberty (equal rates prior).
- This finding is consistent across cultures, suggesting a biological factor.

What causes a depressive episode?

Diathesis

Genetic vulnerability (stress response, plasticity genes)

Previous life experiences

- Early life stressors can promote vulnerability
- Moderate stress experience can build resilience

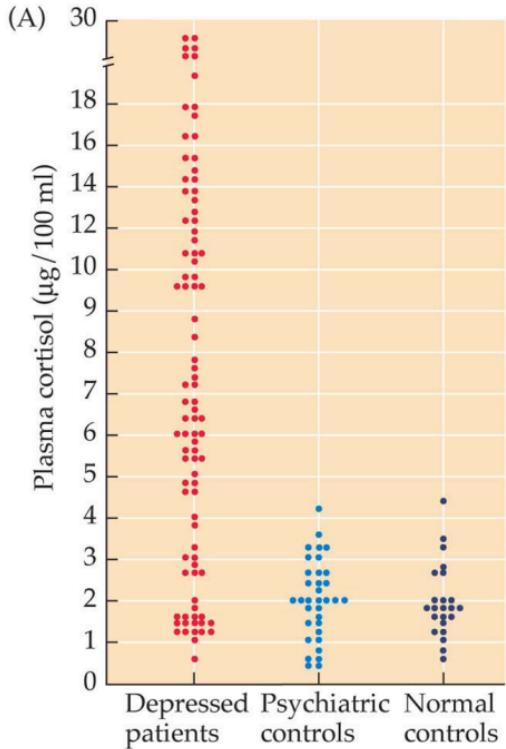
Some effects of stress may even be heritable

- Experience-dependent germline DNA methylation may affect gene expression in offspring

Stress

Current and recent environmental stressors

Stress and depression



The stress response is overactive in 50% of patients with major depression

Plasma (blood) cortisol levels are chronically elevated

The stress response

How does the body respond to stress?

How is the stress response adaptive in the short term?

How does a chronically elevated stress response change the brain?

How might brain changes due to stress promote mental illness?

The stress response

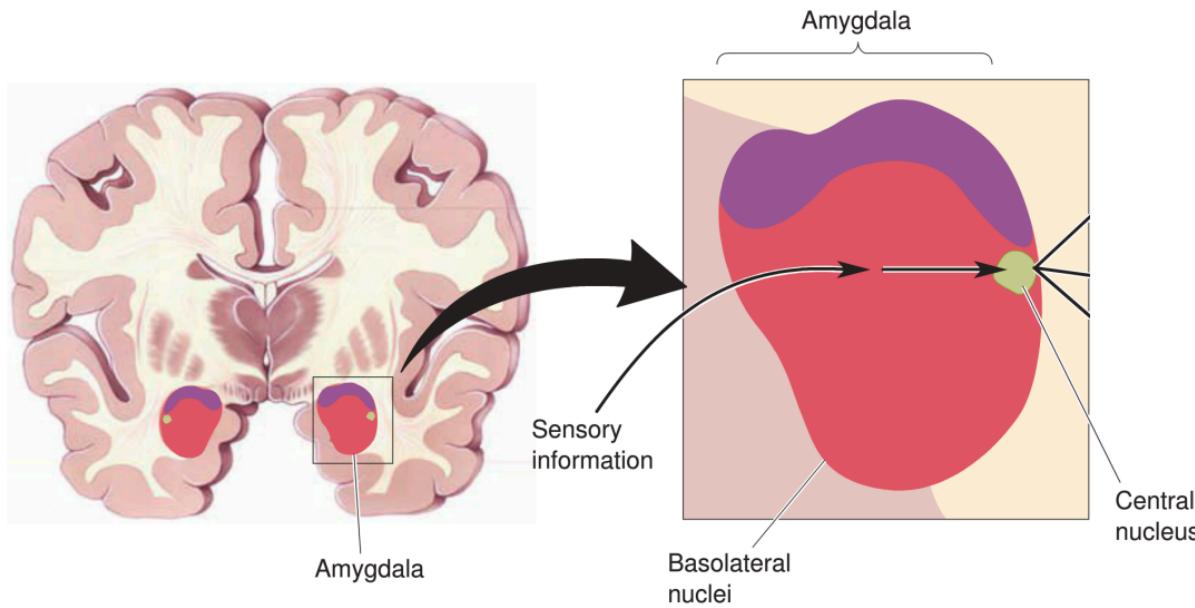
Coordinated reaction to threatening stimuli:

- Increased vigilance and arousal
- Sympathetic autonomic activation
- Release of stress hormones



The amygdala and the stress response

HPA = hypothalamic-pituitary-adrenal axis



The Hypothalamic-Pituitary-Adrenal (HPA) Axis

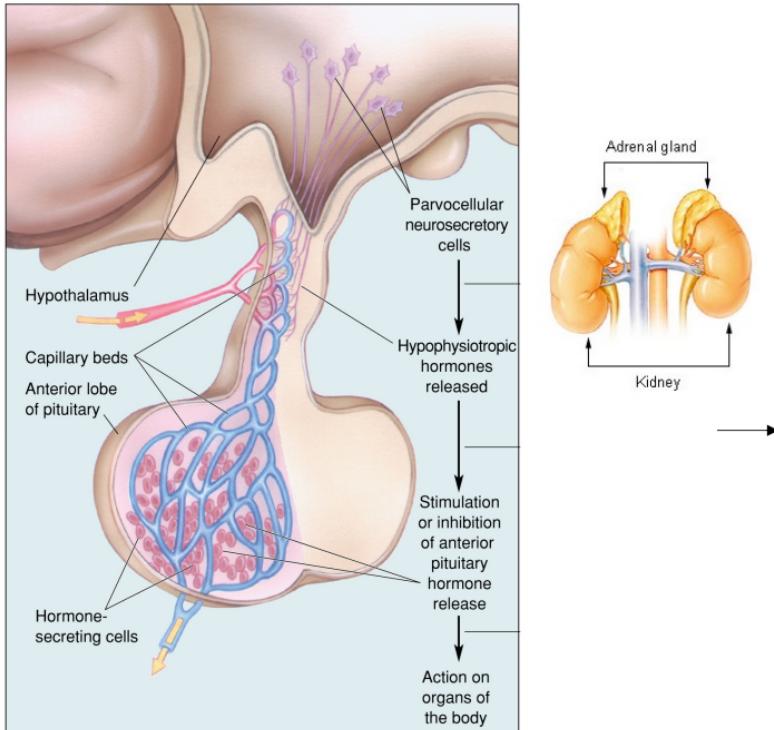


Table 15.1 Hormones of the Anterior Pituitary

HORMONE	TARGET	ACTION
Follicle-stimulating hormone (FSH)	Gonads	Ovulation, spermatogenesis
Luteinizing hormone (LH)	Gonads	Ovarian, sperm maturation
Thyroid-stimulating hormone (TSH); also called thyrotropin	Thyroid	Thyroxin secretion (increases metabolic rate)
Adrenocorticotrophic hormone (ACTH); also called corticotropin	Adrenal cortex	Cortisol secretion (mobilizes energy stores; inhibits immune system; other actions)
Growth hormone (GH)	All cells	Stimulation of protein synthesis
Prolactin	Mammary glands	Growth and milk secretion

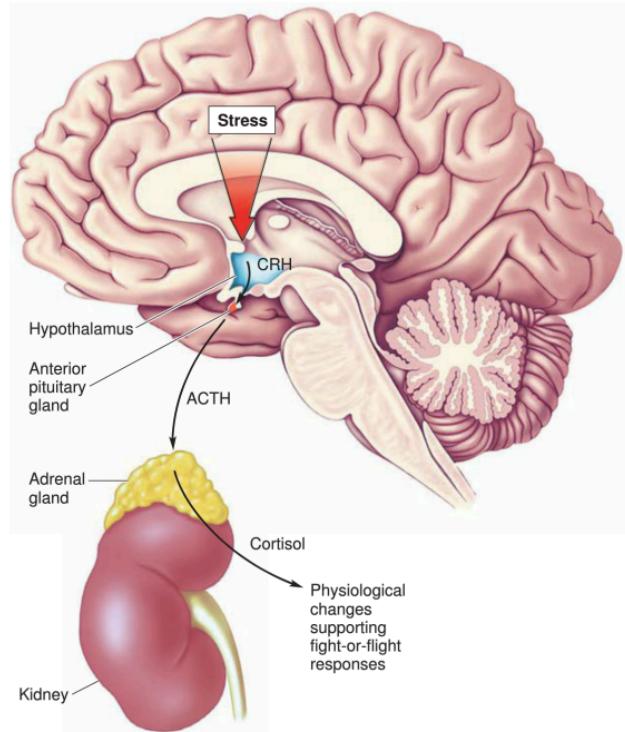
Hypothalamic-pituitary-adrenal (HPA) axis

Under stressful conditions, neurons in the paraventricular nucleus of the hypothalamus secrete **corticotropin-releasing hormone (CRH)** into the anterior pituitary circulation.

This triggers the release of **adrenocorticotropic hormone (ACTH)** from the anterior pituitary into the bloodstream.

ACTH stimulates the release of **cortisol** from the adrenal cortex of the kidney.

Cortisol induces behavioral and physiological changes that allow animals to respond to stressors.

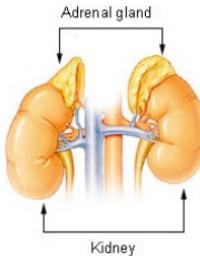


Cortisol

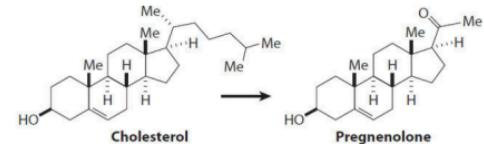
Glucocorticoid steroid hormone

- Regulates glucose metabolism
- Synthesized from cholesterol in the **cortex** of the adrenal gland
- Steroid hormone
 - Lipophilic – can pass through cell membranes, blood-brain barrier

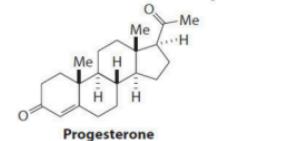
Location	Layer	Significant Hormones
Deepest	Medulla	Epinephrine
Deepest cortical layer	Zona reticularis	Adrenal androgens, for example, androstenedione
Middle cortical layer	Zona fasciculata	Glucocorticoids, for example, cortisol
Superficial cortical layer	Zona glomerulosa	Mineralocorticoids, for example, aldosterone



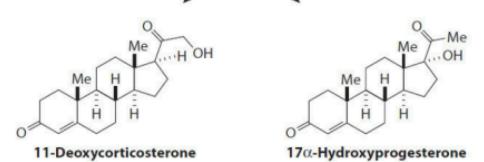
mineralocorticoid



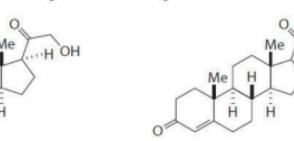
Pregnenolone



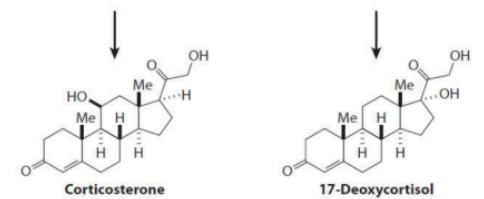
Progesterone



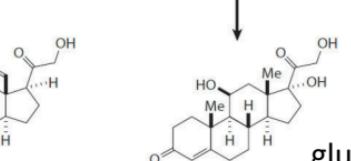
11-Deoxycorticosterone



17 α -Hydroxyprogesterone

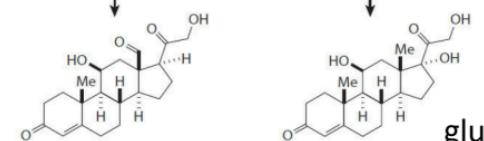


Corticosterone



Aldosterone

glucocorticoid



Cortisol

Glucocorticoid hormone functions

Prepares the organism for action (fight-or-flight):

- Glucose released from energy stores into the blood
- Sympathetic tone increased
 - higher blood pressure, heart rate, breathing rate
 - release of epinephrine/adrenaline from adrenal medulla
- Heightens arousal and vigilance
- Increased blood flow to muscles

Suppresses energy use for restorative purposes:

- Suppresses immune system (metabolic cost)
- Decreases blood flow to gut
- Suppresses sleep

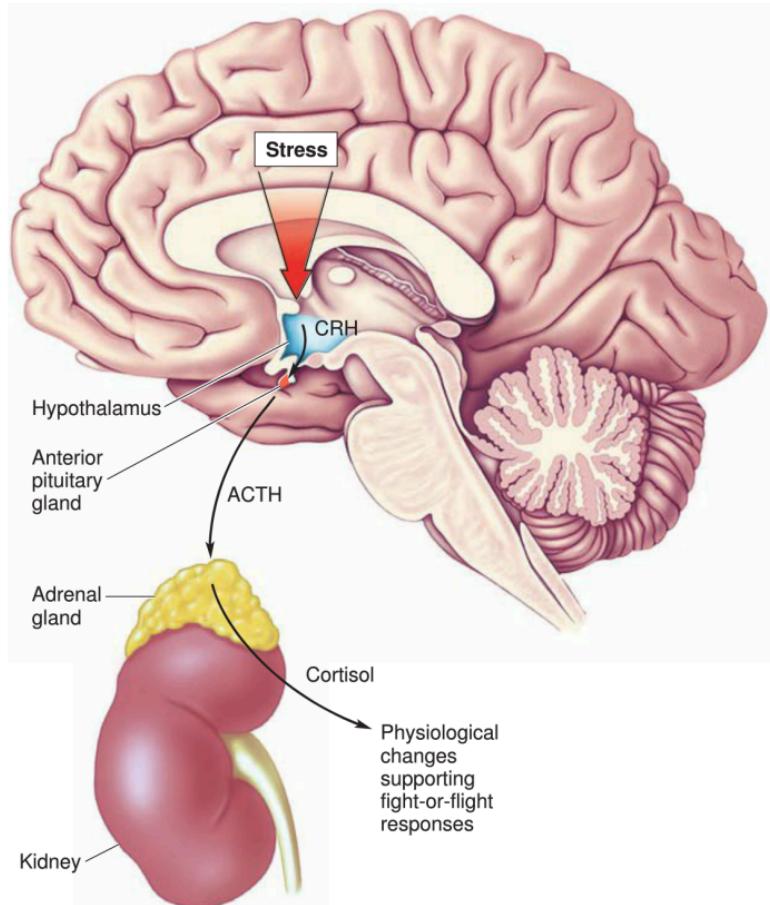
HPA axis activation

Blood cortisol

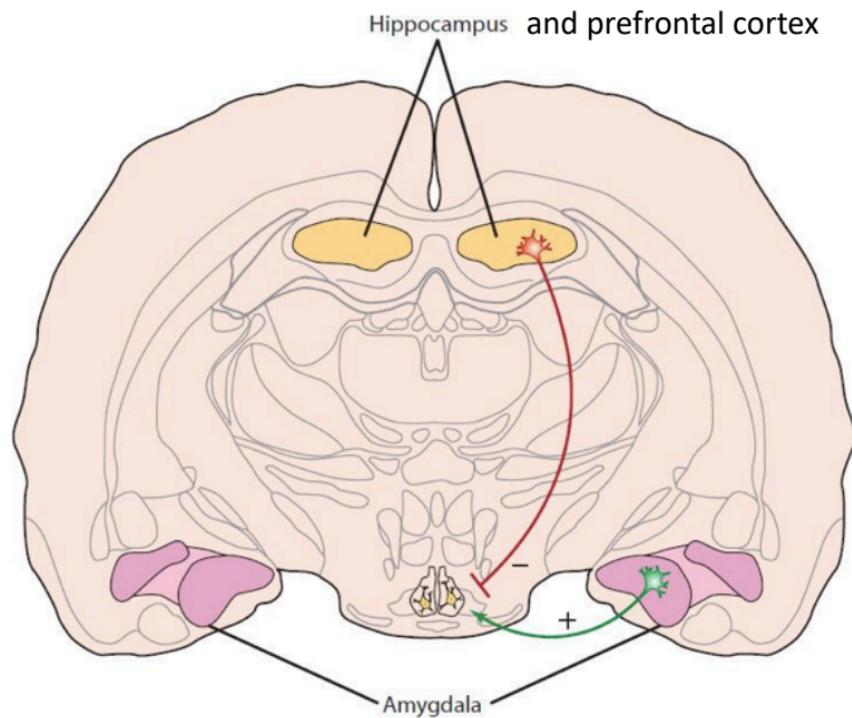
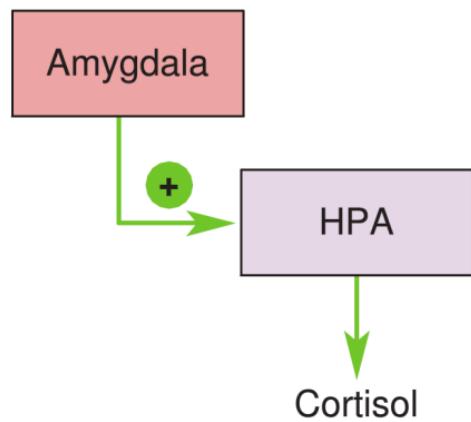
- Elevated after a few minutes
- Peaks at 30 minutes
- Back to baseline after an hour

Negative feedback inhibition

- Importantly, cortisol negatively regulates its own secretion
- Cortisol enhances hippocampal and prefrontal suppression of CRH neural activity in the hypothalamus
- This dampens the HPA axis



Regulation of the HPA axis



What if stress is prolonged?

Glucocorticoid hormone functions

Prepares the organism for action (fight-or-flight):

- Glucose released from energy stores into the blood
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 - higher blood pressure, heart rate, breathing rate
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Prolonged exposure to cortisol changes the brain

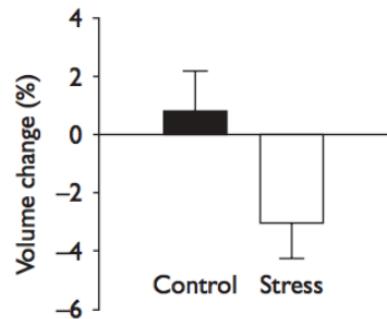
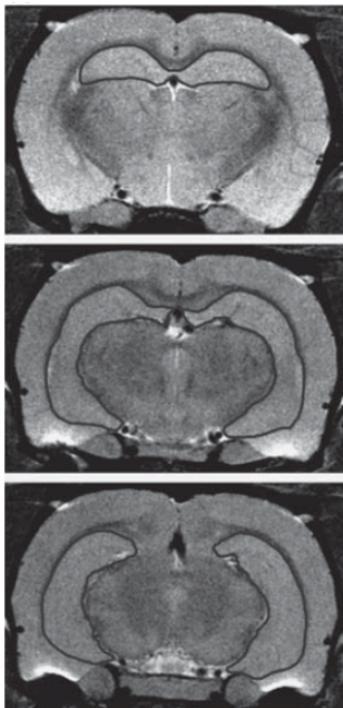
Decreased brain volume

Decreased dendritic complexity

- hippocampus
- prefrontal cortex

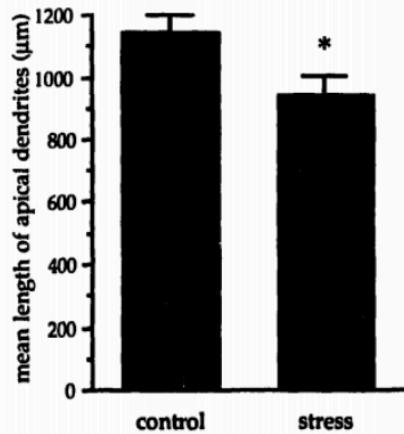
Reduction in the production of new neurons (neurogenesis) in the hippocampus

Stress reduces hippocampal volume

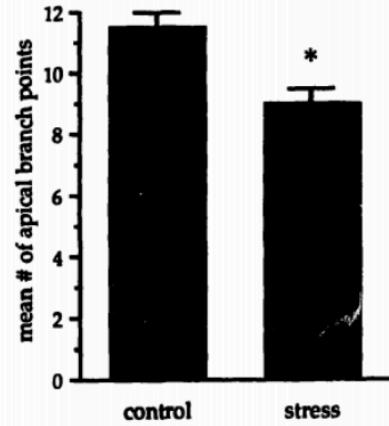


Chronic stress reduces hippocampal and prefrontal dendritic branch length

A

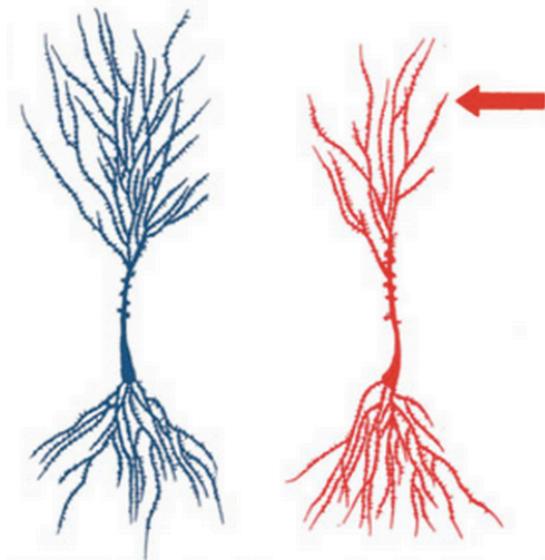


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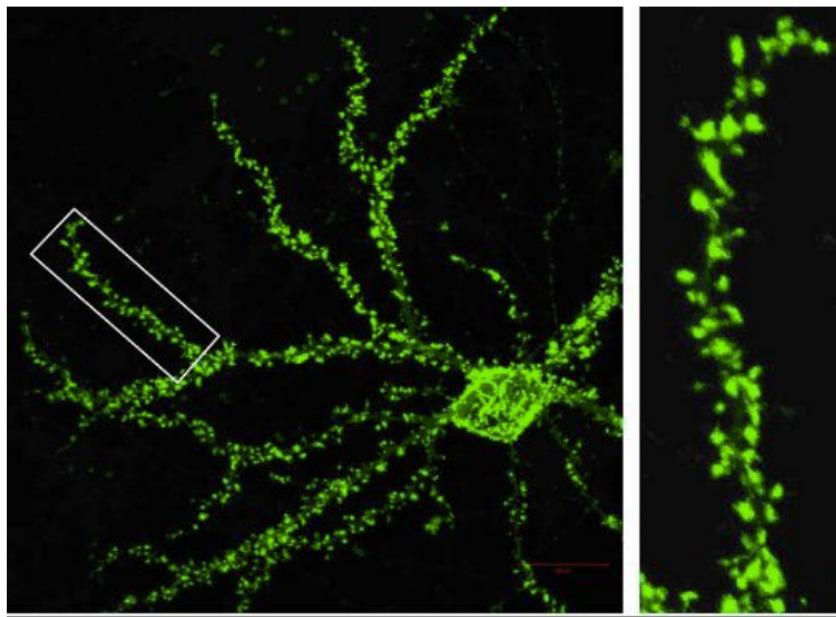


Control

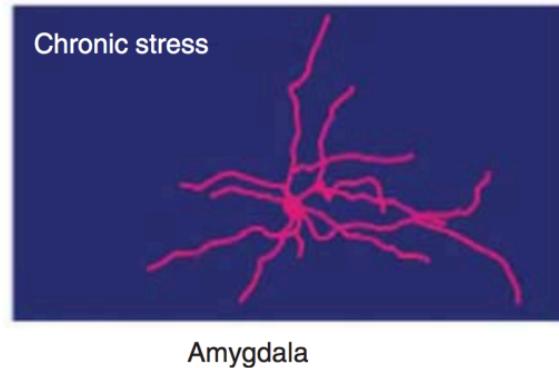
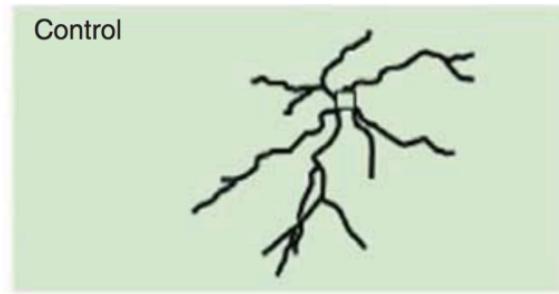
Stress



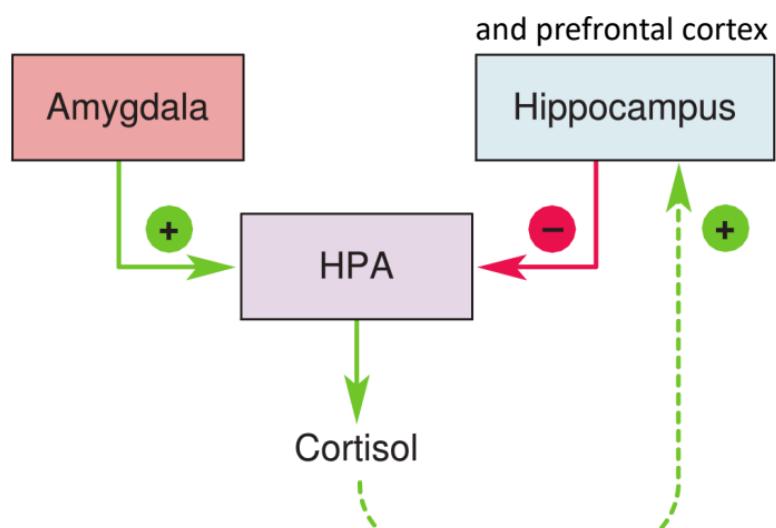
Chronic stress reduces number of hippocampal and prefrontal dendritic spines



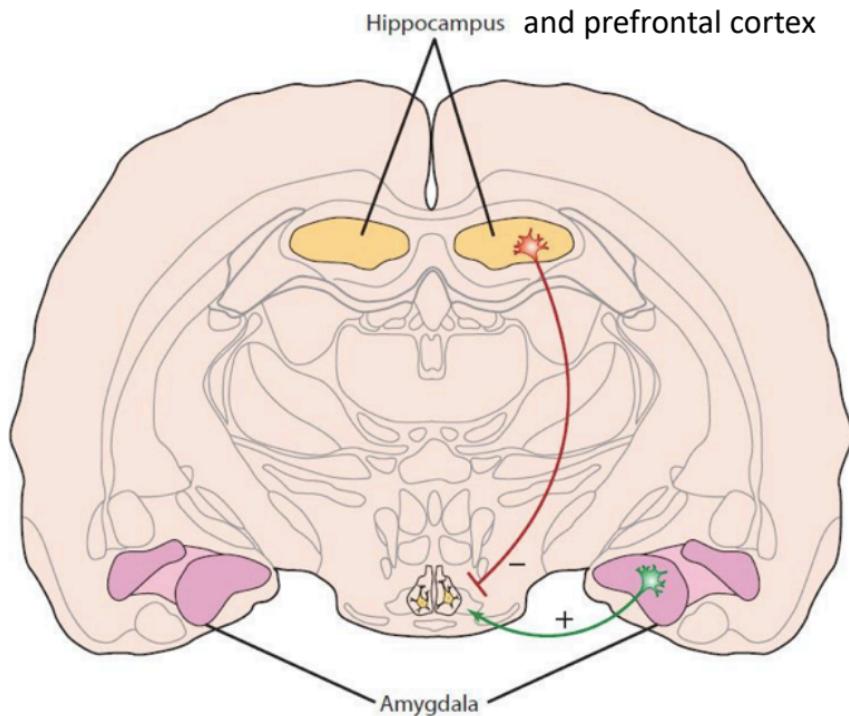
Chronic stress *increases* amygdala dendritic branch length



Chronic stress promotes HPA axis activation



Sustained high-stress state



Treatments for depression

Antidepressant drug therapy

Selective serotonin reuptake inhibitors (Prozac)

Norepinephrine-Dopamine reuptake inhibitors (Wellbutrin)

Anesthetic agents (Ketamine) – fast acting new treatment



Electroconvulsive therapy (circa 1940s)



Electrically induced seizure used for the treatment of severe depression

Used with patients who have not responded to antidepressant medication or are suicidal

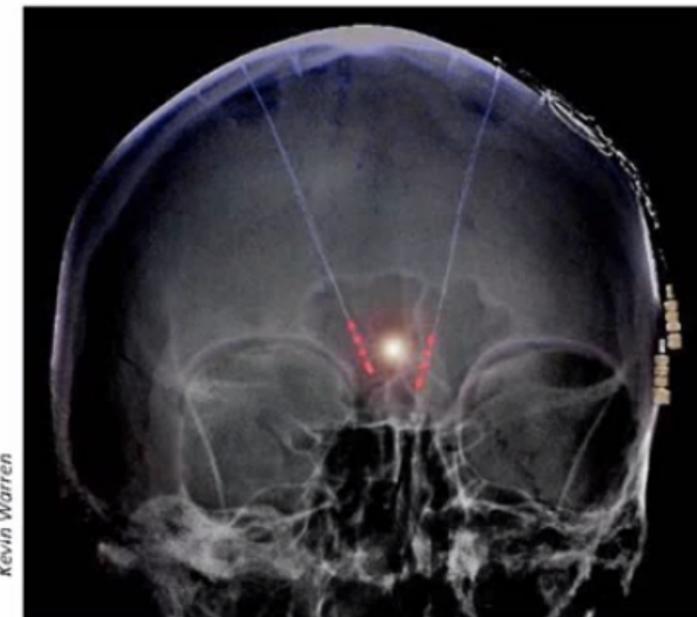
Applied every other day for ~2 weeks

Side effects: memory loss (retrograde amnesia), but can be minimized if shock is localized to right hemisphere



How does ECT work? Remains unknown, but may alter the expression of genes in the hippocampus and the frontal cortex. Increases serum BDNF.

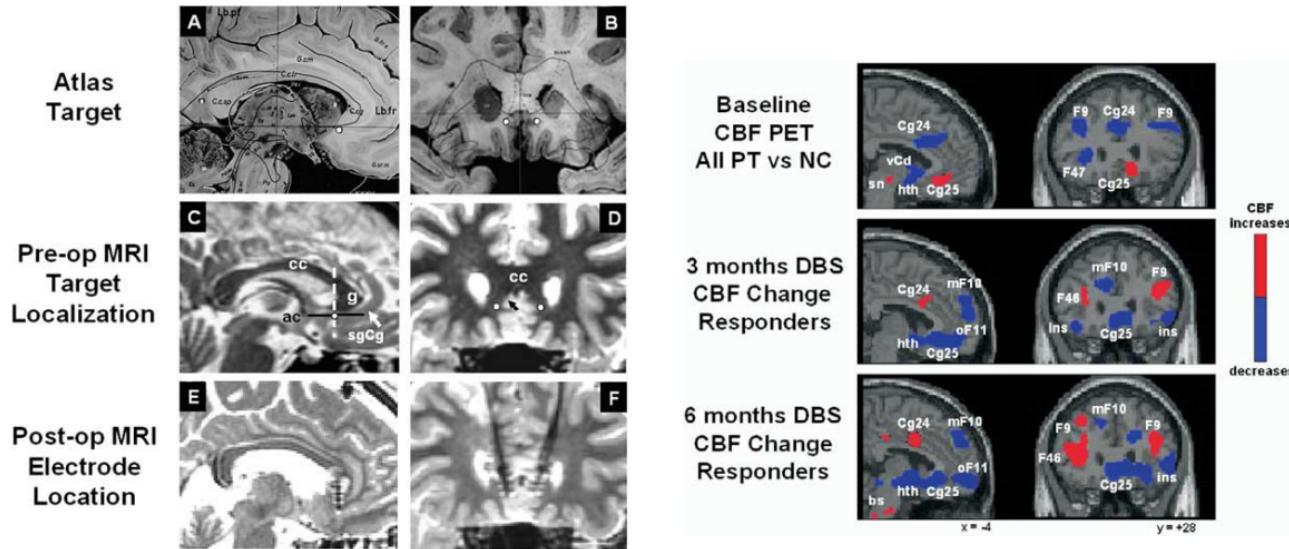
Subgenual cingulate DBS for depression



Kevin Warren

Mayberg 2014

Deep brain stimulation in the subgenual cingulate is therapeutic in treatment-resistant depression



Imaging studies show elevated subgenual cingulate activity in depressed patients, which is reduced after therapeutic DBS.

Good luck on the exam!