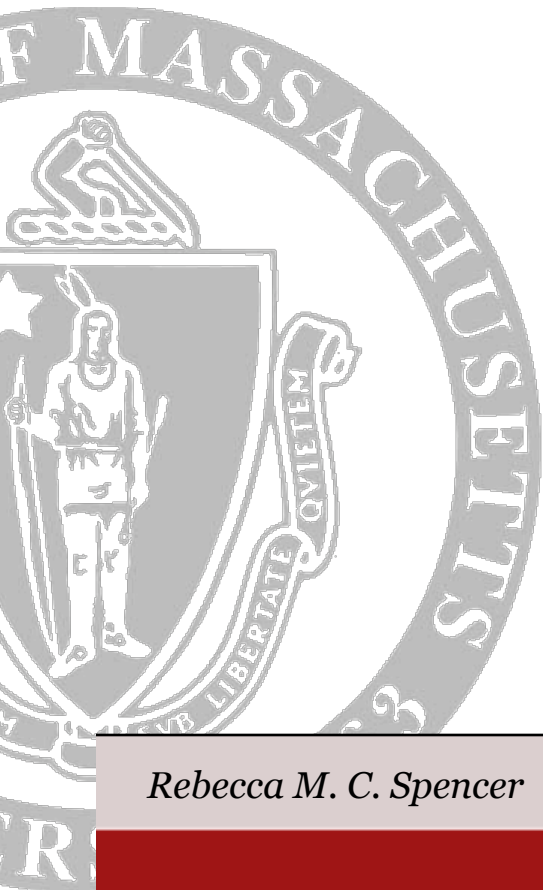


Neurobiology of brain dysfunction

Post-traumatic stress disorder (PTSD)



PTSD - Epidemiology

Trauma exposure:

- 50-60% of general population exposed to trauma.
- 56% men; 49% women exposed to >1 trauma.
- 90% exposure in some high risk urban areas.

PTSD - diagnosis

A. Traumatic event:

- Must have involved risk of life or injury to self or others
- Must have elicited an response of fear or helplessness

B. Re-experiencing: must invoke response of flashbacks, recurring dreams, or emotional response to similar stimuli

C. Avoidance/Numbing

D. Increased arousal: difficulty sleeping, anger problems, etc

E. Symptoms >1 month

F. Must have clinical impact

PTSD - Epidemiology

PTSD (lifetime):

- 7-8% general population
(Kessler et al. 1995, *Arch Gen Psych*)

- Combat veterans higher:
 - 30% using liberal estimate
(Kulka et al., 1990)

 - 19% using conservative estimate
(Dohrenwend et al., *Science*, 2006)

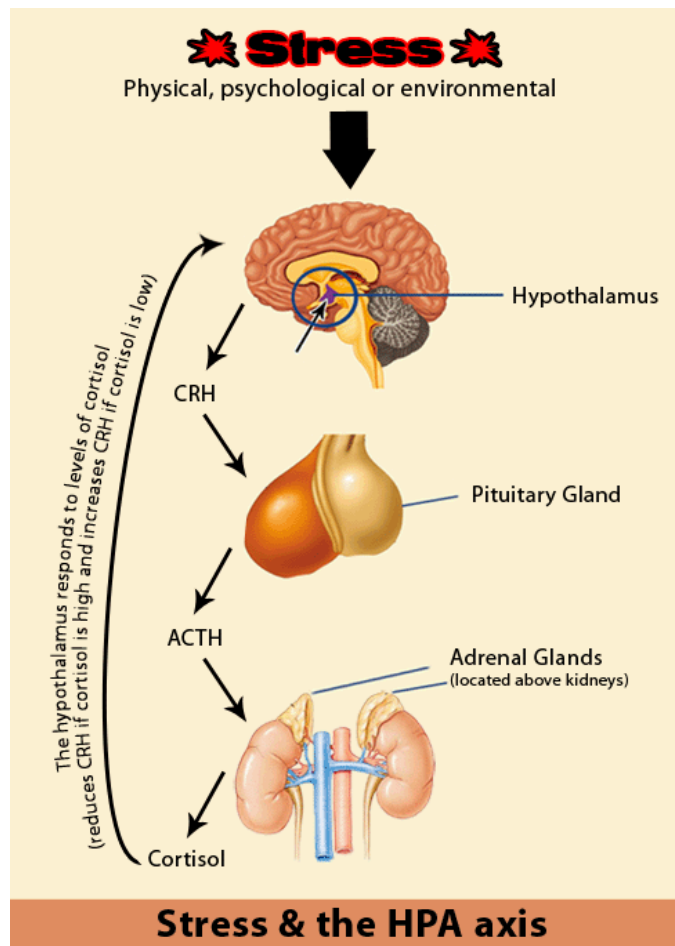
Post-traumatic stress disorder (PTSD)

Stress ≠ **Trauma**

Exposure ≠ **PTSD**

Acute ≠ **Chronic**

Normal stress response



- Stress
- CRF released from hypothalamus
- Transported to pituitary
- Where it stimulates production of ACTH
- Causing synthesis/secretion of glucocorticoids from adrenal glands

Normal stress response

- Glucocorticoid functions:
 - Immune:
 - ↑ Anti-inflammatory proteins
 - ↓ Pro-inflammatory proteins
 - Metabolic:
 - Synthesize glucose
 - Inhibit uptake of glucose from muscles and fat
 - Stimulate fat breakdown

(collectively, maintain normal glucose)

Normal & abnormal stress response

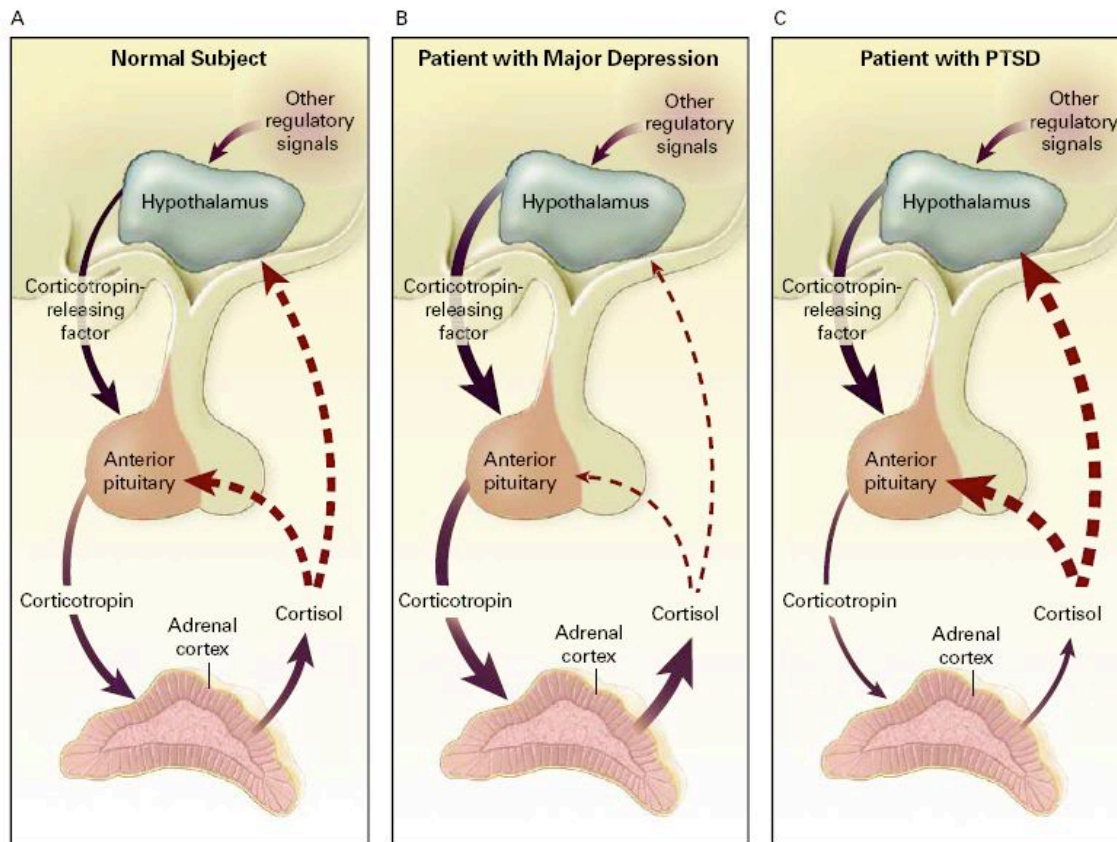


Figure 1. Response to Stress in a Normal Subject (Panel A), a Patient with Major Depressive Disorder (Panel B), and a Patient with PTSD (Panel C).

In normal subjects (Panel A) and in patients with major depression (Panel B), brief or sustained periods of stress are typically associated with increased levels of both cortisol and corticotropin-releasing factor. In each panel the thickness of the interconnecting arrows denotes the magnitude of the biologic response. Corticotropin-releasing factor stimulates the production of corticotropin, which in turn stimulates the production of cortisol. Cortisol inhibits the release of corticotropin from the pituitary and the release of corticotropin-releasing factor from the hypothalamus. It is also responsible for the containment of many stress-activated biologic reactions. In patients with PTSD (Panel C), levels of cortisol are low and levels of corticotropin-releasing factor are high. In addition, the sensitivity of the negative-feedback system of the hypothalamic-pituitary-adrenal axis is increased in patients with PTSD rather than decreased, as often occurs in patients with major depression.³¹

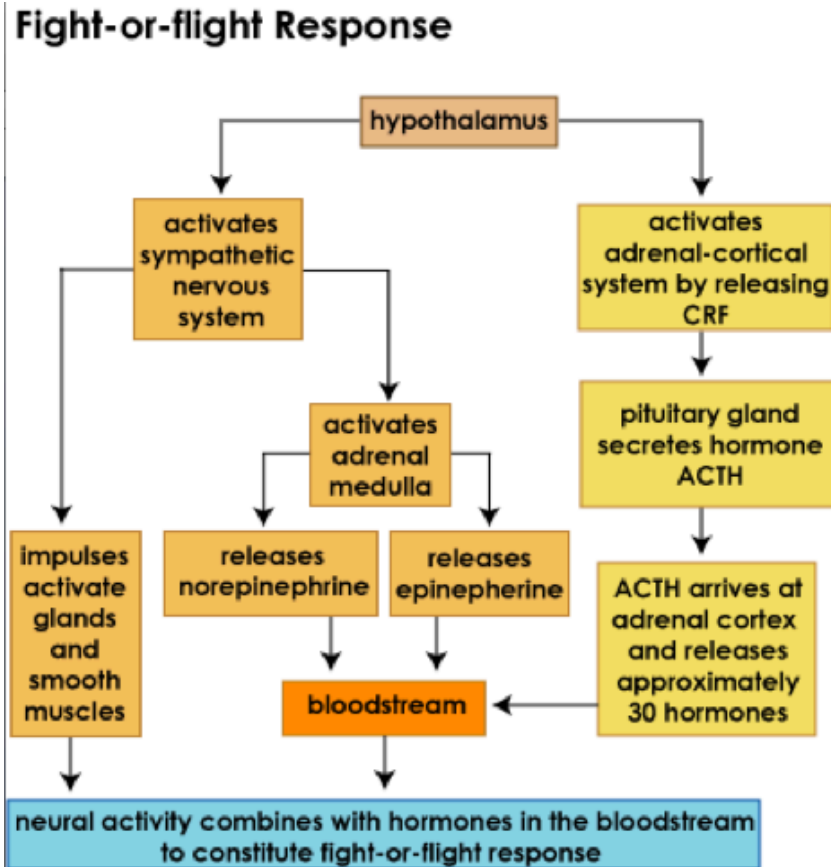
PTSD:

- Increased CRF
- Decreased ACTH
- Decreased cortisol

HPA Theory of PTSD:

PTSD = hypocortisolemia
Due to exaggerated HPA
negative feedback

Stress response

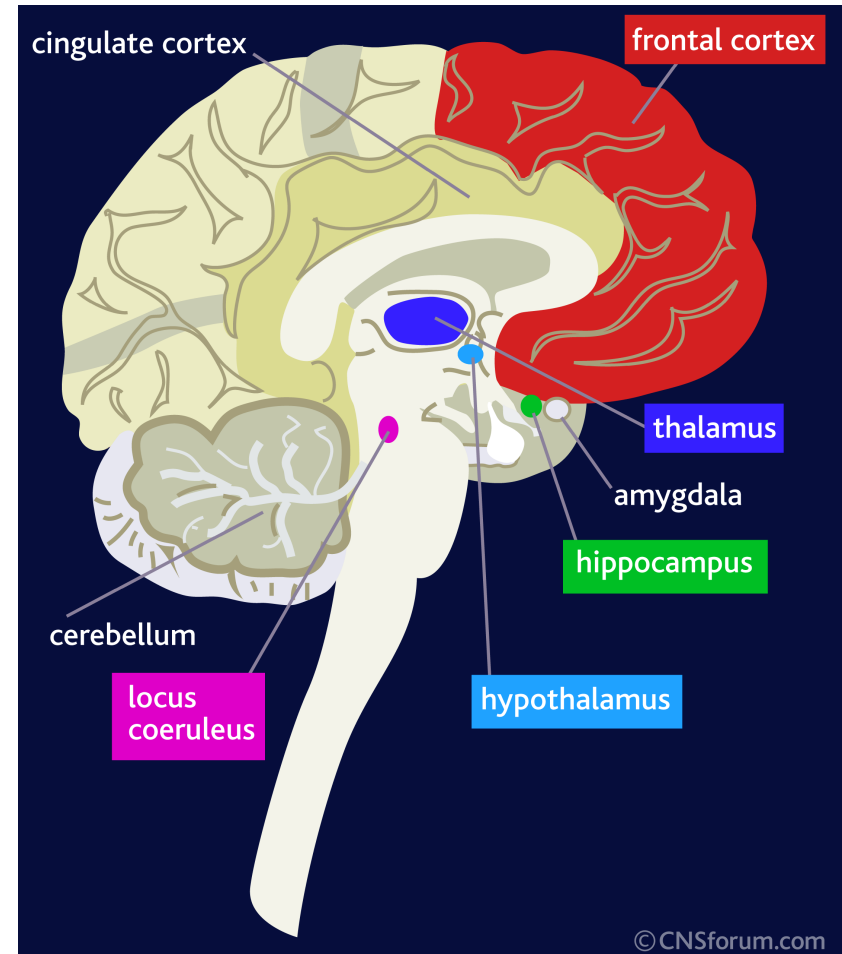


NE Theory of PTSD:

Hyperactivity in the NE system.
 Baseline NE is normal
 With stress (trauma related stimuli), the NE response is overactive

PTSD - neuroimaging

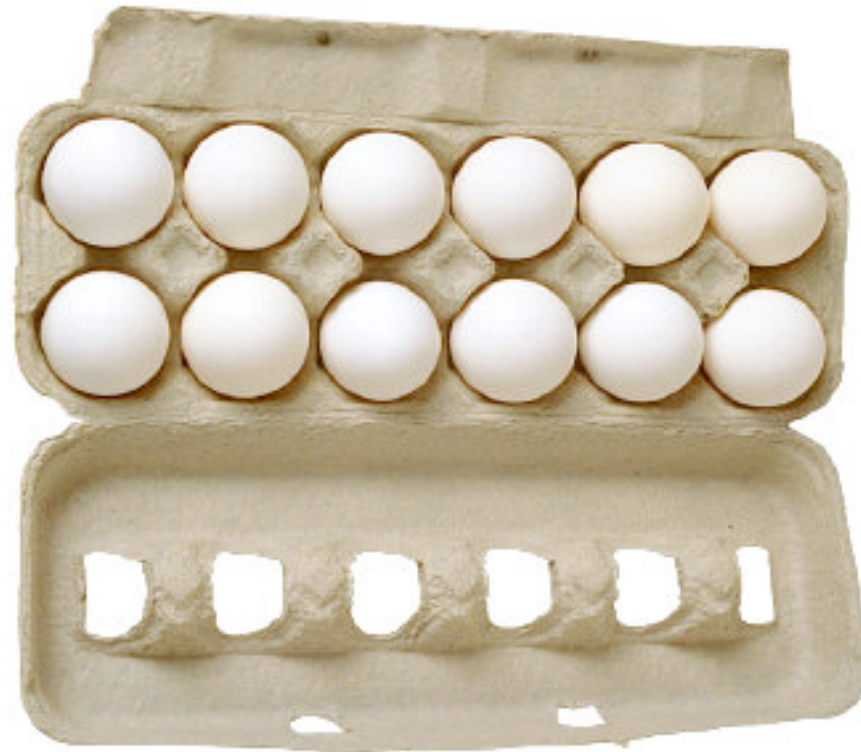
- Structural
 - ↓ hippocampus
 - ↓ medial PFC
- Functional
 - ↑ amygdala
 - ↓ medial PFC
- Biochemical
 - ↓ hippocampus
 - ↓ ACC, ↓ PFC



PTSD – Neuropsychological correlates

- Verbal intellectual
- Sustained attention
- Working memory
- Inhibition
- New learning/memory

What came first?



PTSD - genetics

Those with PTSD have reduced hippocampus volume.

So:

- Does PTSD reduce hippocampus volume

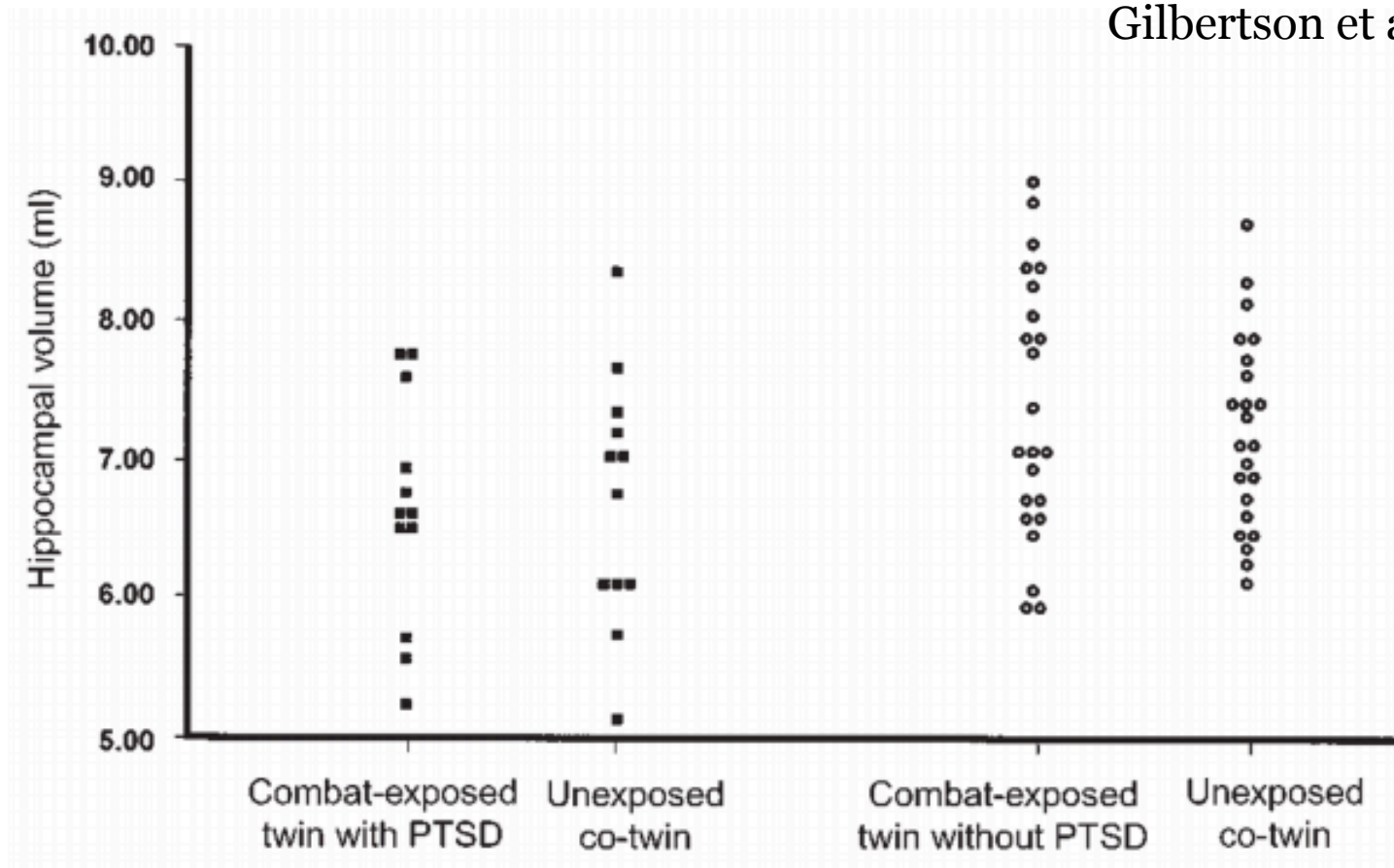
OR

- does small hippocampus make you susceptible to PTSD

???

PTSD - genetics

Gilbertson et al., 2002



PTSD - treatment

- Cognitive Behavioral Therapy (CBT) with:
 - Exposure therapy (represent the threat)
 - Cognitive restructuring (interpreting how the event unfolded)
 - Stress inoculation training (train to reduce anxiety)

PTSD – treatment

- Pharmacological: **Treat symptoms**
- FDA approved for PTSD
 - Sertraline (Zoloft)
 - Paroxetine (Paxil)
 - Both are SSRIs/anti-depressants: Decrease serotonin reuptake at the presynapse so the post-synaptic gets more
- Other:
 - Benzos: Relaxes, improves sleep
 - Antipsychotics
 - Other anti-depressants: Prozac, Celexa