Outline

A. Stress-related Psychiatric Disorders
   1. Emotional Circuitry: Key Components
   2. The Hypothalamic Pituitary Adrenal (HPA) Axis

B. Neurodegenerative Disorders: Alzheimer’s Disease
   1. Biomarkers & Ethics
Stress-related Psychiatric Disorders: Examples

**Major Depression**¹
- 15 million in US & growing globally
- Current standard of care: SRIs/NRIs, 60% of patients do not respond

**Post-Traumatic Stress Disorder (PTSD)**²
- 8 million in US, a priority indication for military medicine
- Major Depression, Intermittent Explosive Disorder, Impulse Control Disorders are co-morbid
- Current standard of care: repurposed SSRIs

¹ Mathew & Charney (2009); NIMH ² NIMH; USAMRMC
Basic Neurobiology & Physiology
Anatomical Circuits in Mood Disorders: Medial Prefrontal Network & Amygdala

Price & Drevets (2010)
Limbic System: Emotional Circuitry

**Left:** diagram of amygdaloid circuits involving the striatum, pallidum, medial thalamus and prefrontal cortex and output to the hypothalamus and brainstem. **Right:** diagram of areas of the cerebral cortex that receive axonal projections from the amygdala. The dark, medium, and lightly shaded areas represent high, medium, and low density of amygdaloid fibers. In Price & Drevets, 21010, modified from Amaral et al, 1992.
Stress: The Hypothalamic-Pituitary-Adrenal Axis
The Hypothalamic-Pituitary-Adrenal Axis

Key Considerations

- Regulatory Peptides
  - CRH
  - AVP

- Feedback Regulation
  - Glucocorticoids

- Rhythm Disturbance
  - Sleep
  - Cardiovascular
  - Core Temperature
  - Activity
Altered Cerebral Blood Flow in Major Depressive Disorder

Price & Drevets (2010)
PTSD: A Complex Disorder with Frequent Co-morbidities

- Major Symptoms
  - Hyperarousal to Traumatic Memory
  - Emotional Dysregulation

- Common co-Morbidities
  - Major Depression
  - Anxiety Disorders
  - Impulsivity/Violent Behavior
  - Substance Abuse
Plasma Vasopressin is Elevated in Combat Veterans with PTSD

In veterans with PTSD (far left)

- PTSD w/o MDD
- PTSD with MDD

Plasma AVP in veterans with PTSD (far left) and controls that were 1) veterans that experienced trauma but not PTSD (TC; center column) or healthy civilians (right)

Plasma AVP in veterans with PTSD (far left) and controls that were 1) veterans that experienced trauma but not PTSD (TC; center column) or healthy civilians (right)

de Kloet et al (2008)
Predatory Conditioned Fear – A Model of PTSD
V1a Receptor Blockade is Effective in a Conditioned Fear Animal Model of PTSD

- V1a antagonist significantly reduced hyperarousal in brain regions mediating fear & memory when given two weeks after traumatic fear conditioning
- Normal fear responses & arousal patterns were unaffected (not shown)
Functional Neuroimaging in PTSD: Negative Emotional States

Hyperactivation

Hypoactivation

AMY: Amygdala
IFG: Inferior Frontal Gyrus

ACC: Anterior Cingulate Cortex
VM PFC: ventromedial prefrontal cortex
Mood Disorders: Medial Prefrontal Network & Amygdala

Price & Drevets (2010)
Thank you for your time and attention