

Diseases of the Nervous System

Neal G. Simon, Ph.D.
Professor, Dept of Biological Sciences
Lehigh University

Outline

A. Stress-related Disorders

1. Emotional Circuitry: Key Components

2. The Hypothalamic Pituitary Adrenal (HPA) Axis

B. Alzheimer's Disease

1. Biomarkers & Ethics

Stress-related CNS Disorders

⬡ Major Depression¹

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

⬡ Intermittent Explosive Disorder²

- 62 million in US
- Current standard of care: no approved treatment, off-label use of SSRIs

⬡ Impulse Control/Anger Disorders

- Core component of borderline personality, antisocial personality, and conduct disorders
 - 12 million in US
- Common co-morbidity impacting therapeutic response in PTSD, ADHD, & psychoses
- Current standard of care: no approved treatment

⬡ Post-Traumatic Stress Disorder (PTSD)³

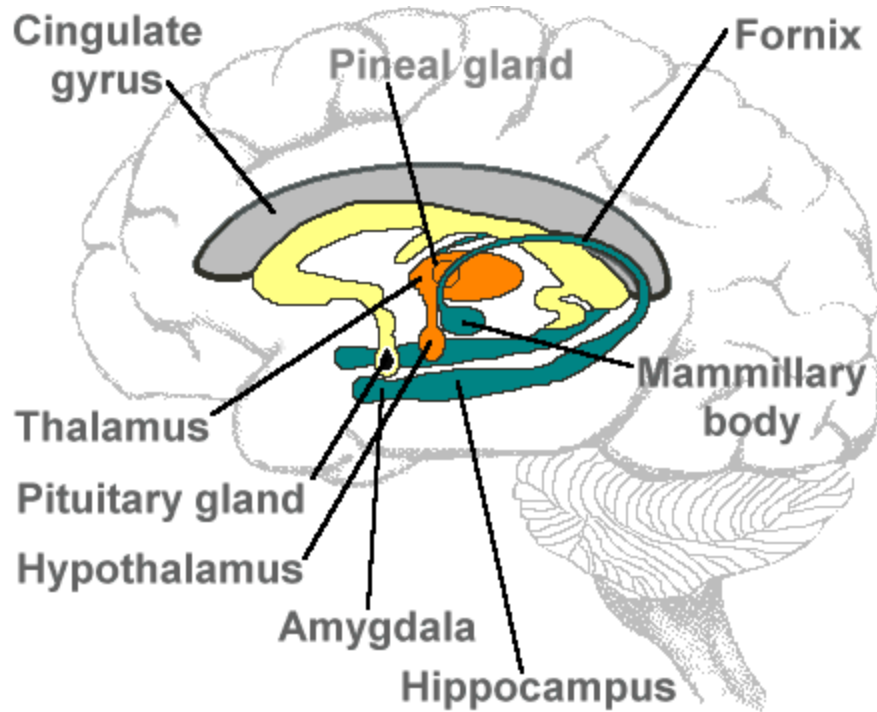
- 8 million in US, a priority indication for military medicine
- Major Depression, Intermittent Explosive Disorder, Impulse Control Disorders are co-morbid
- Current standard of care: repurposed SSRIs

Stress-related Disorders: Disturbed Affect

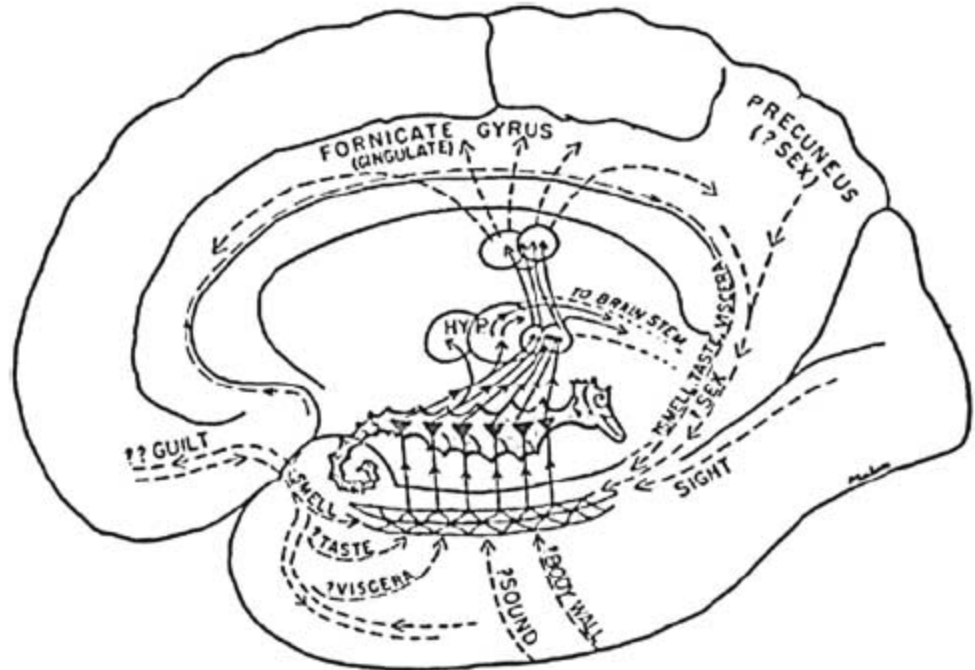


Basic Neurobiology & Physiology

The Emotional Brain

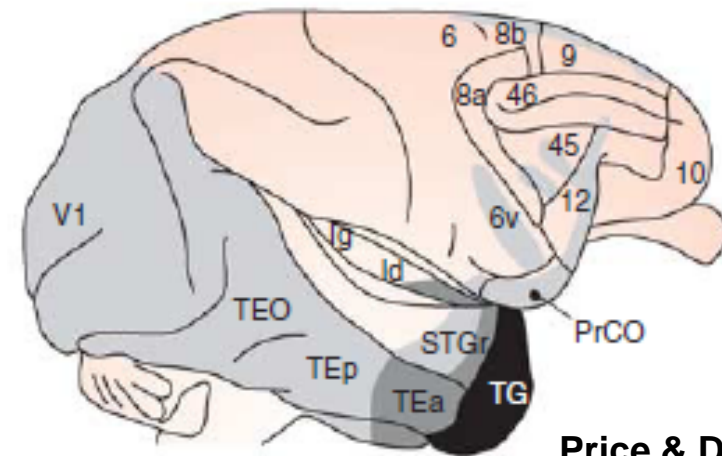
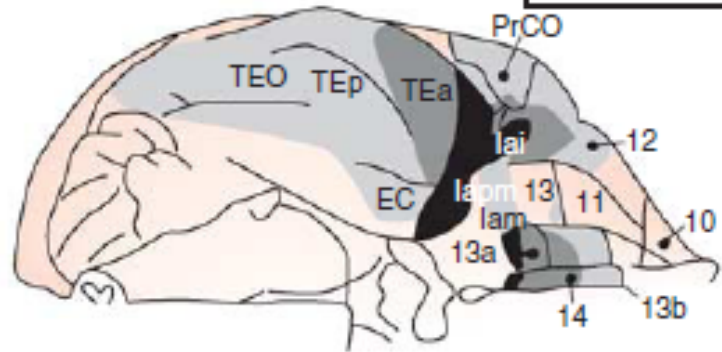
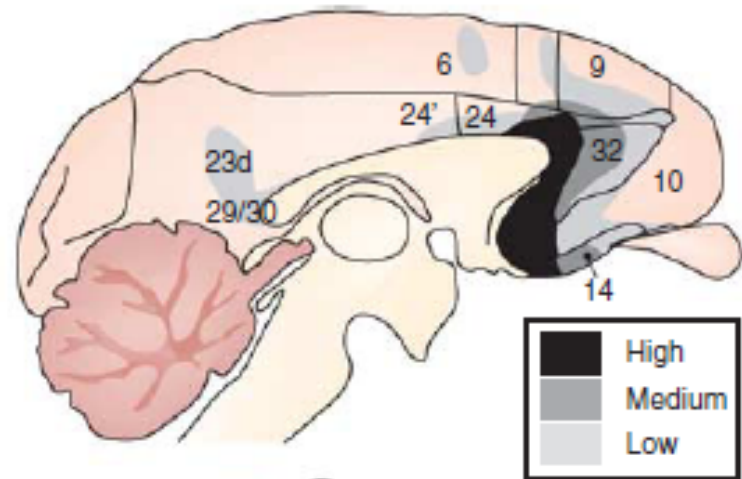
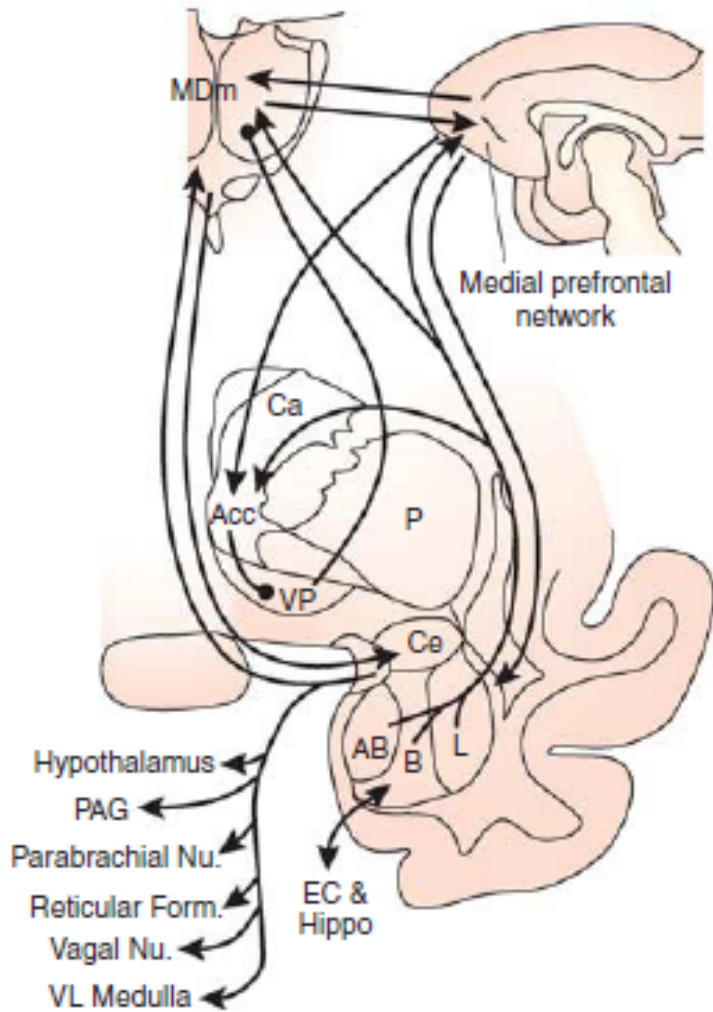


The Limbic System

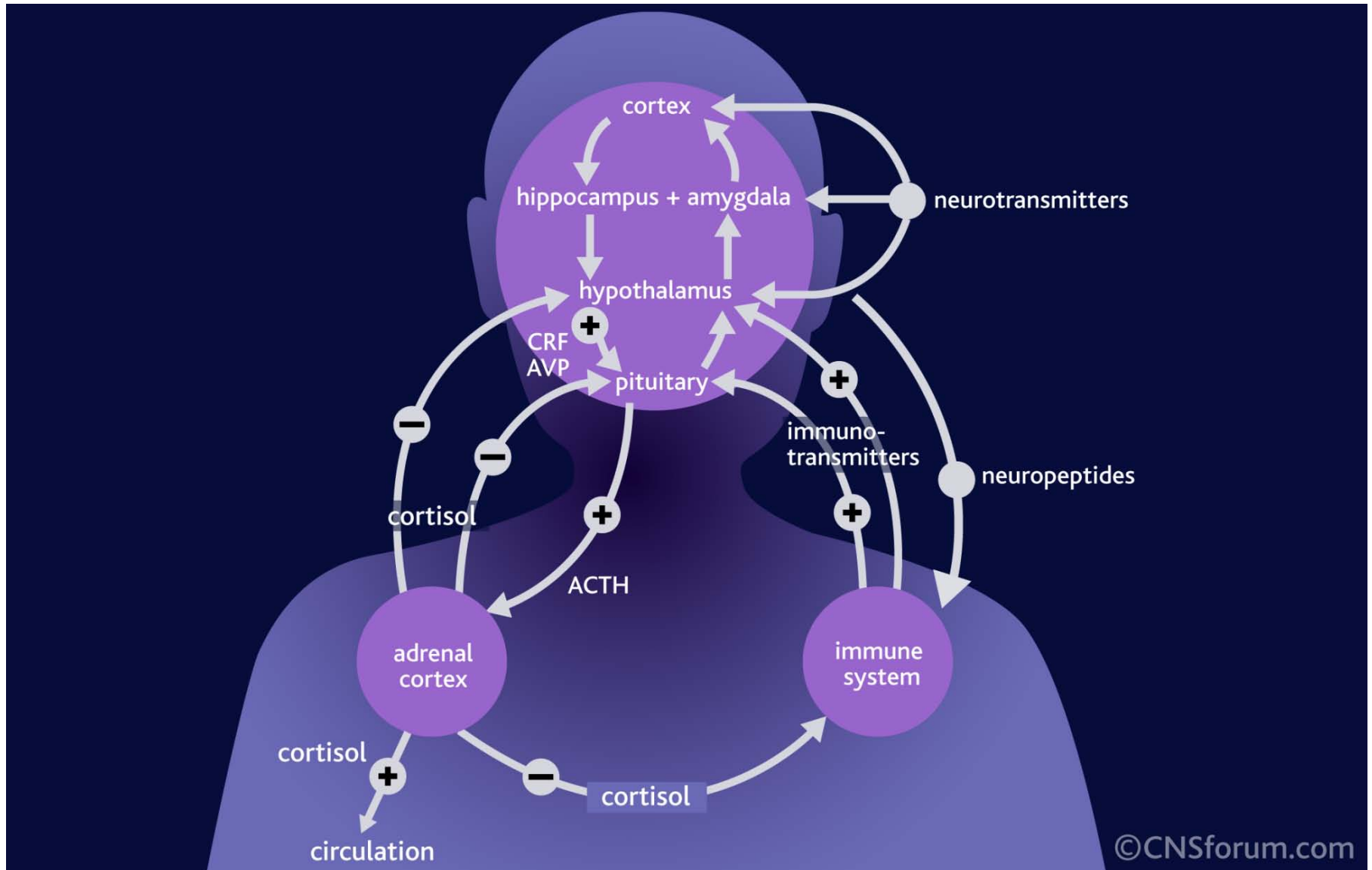


McLean, 1952

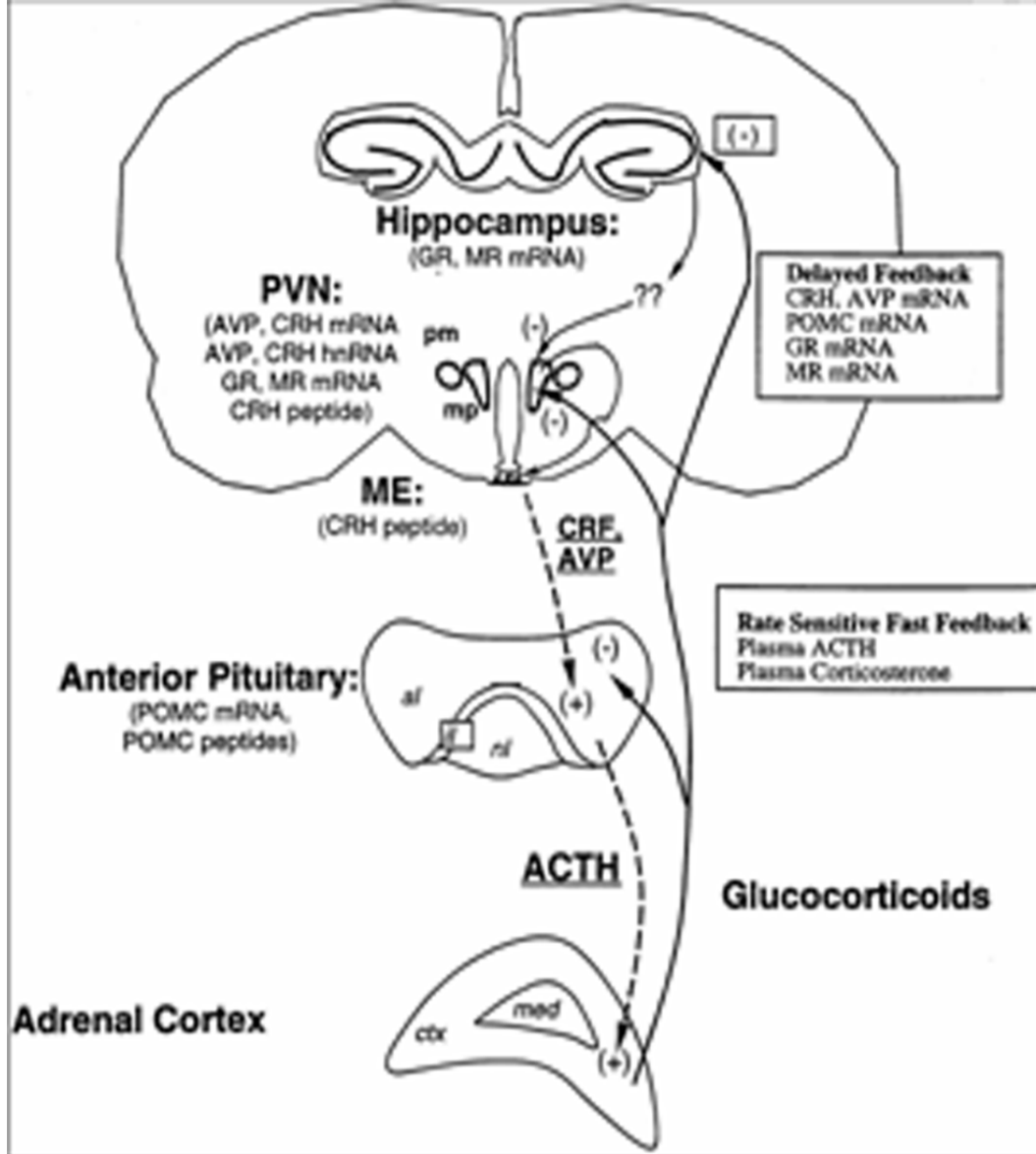
Amygdala: Outputs & Circuits



Hypothalamic-Pituitary-Adrenal Axis



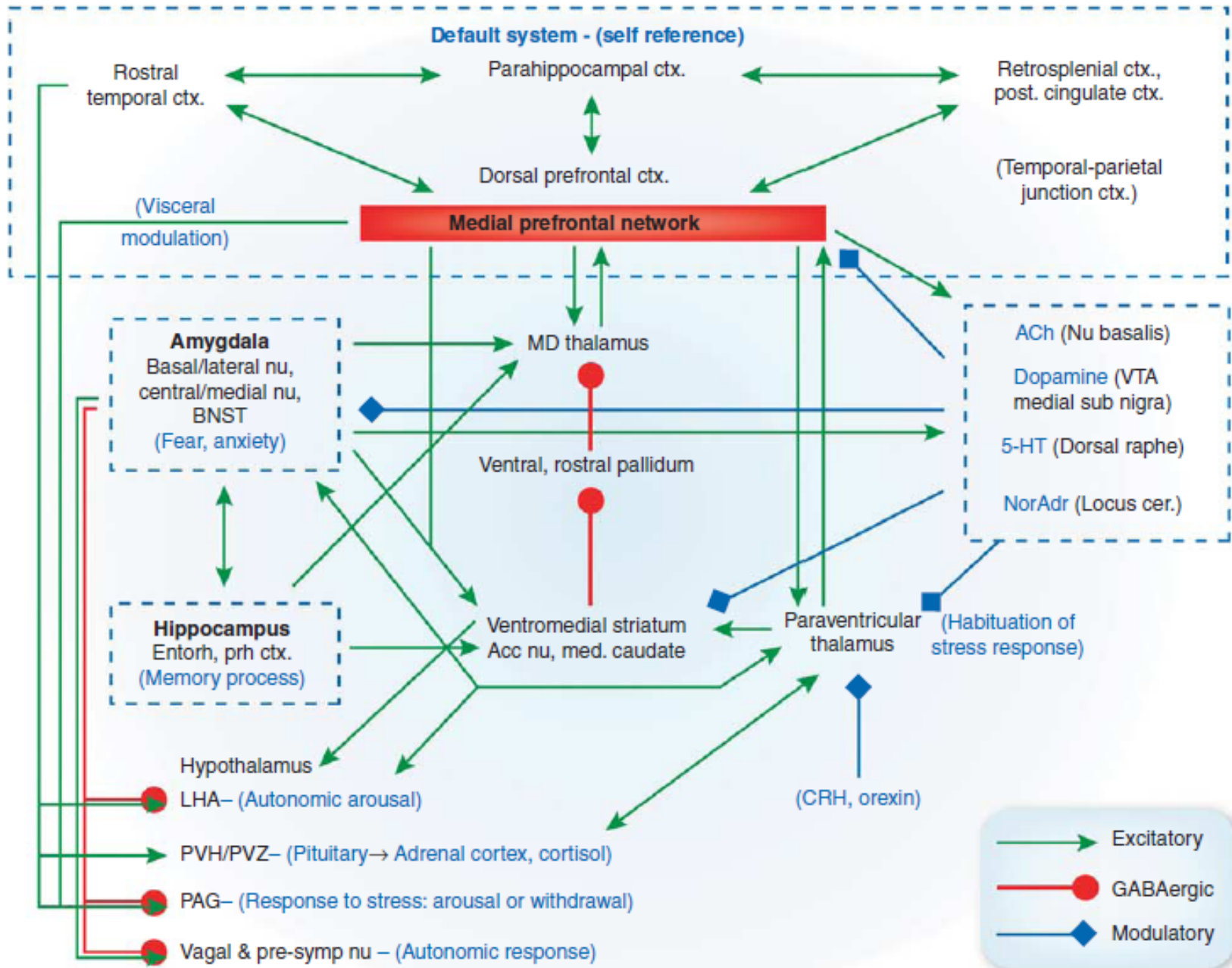
1. The Hypothalamic-Pituitary-Adrenal Axis



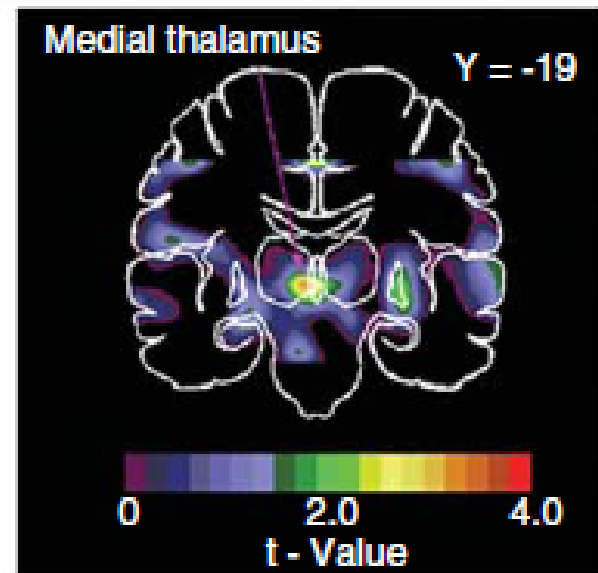
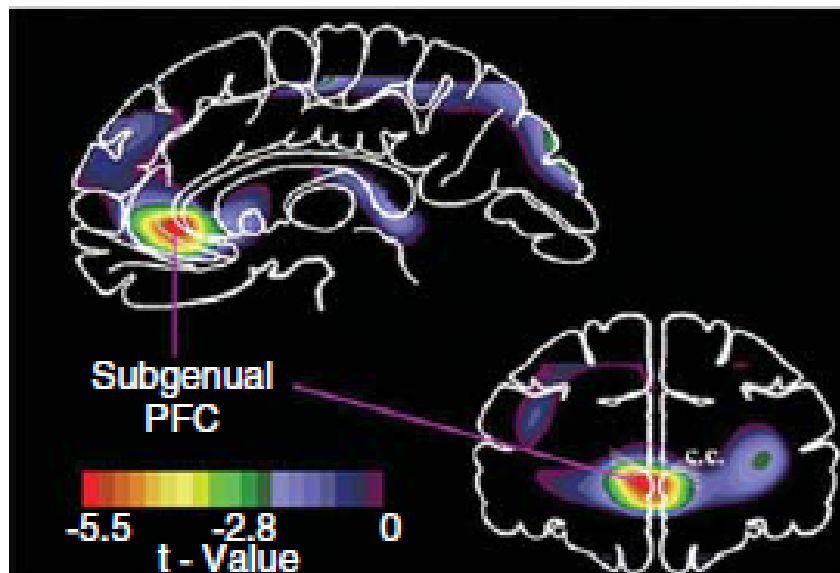
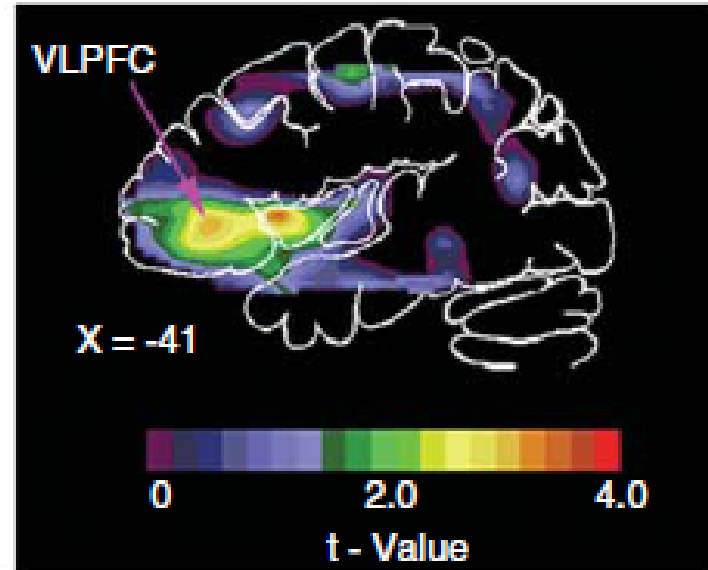
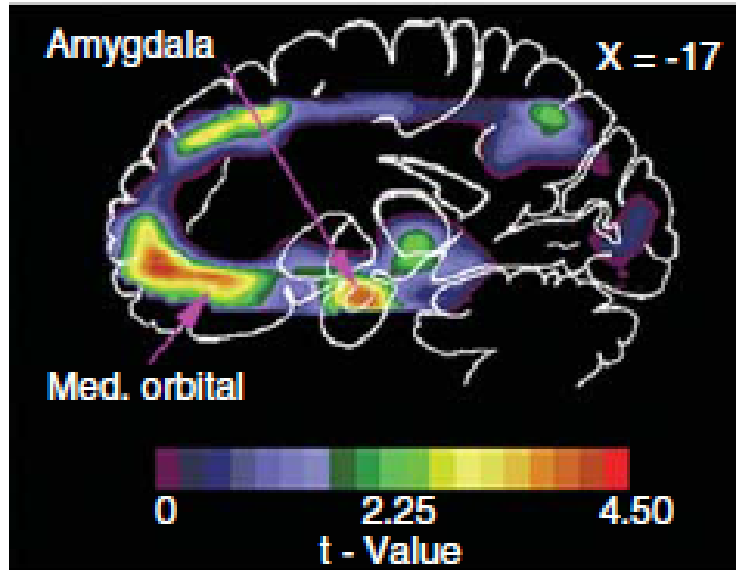
Key Considerations

- **Regulatory Peptides**
 - CRF
 - AVP
- **Feedback Regulation**
 - Glucocorticoids
- **Rhythm Disturbance**
 - Sleep
 - Cardiovascular
 - Core Temperature
 - Activity

Anatomical Circuits in Mood Disorders: Medial Prefrontal Network & Amygdala



Altered Cerebral Blood Flow in Major Depressive Disorder



PTSD: A Complex Disorder with Frequent Co-morbidities

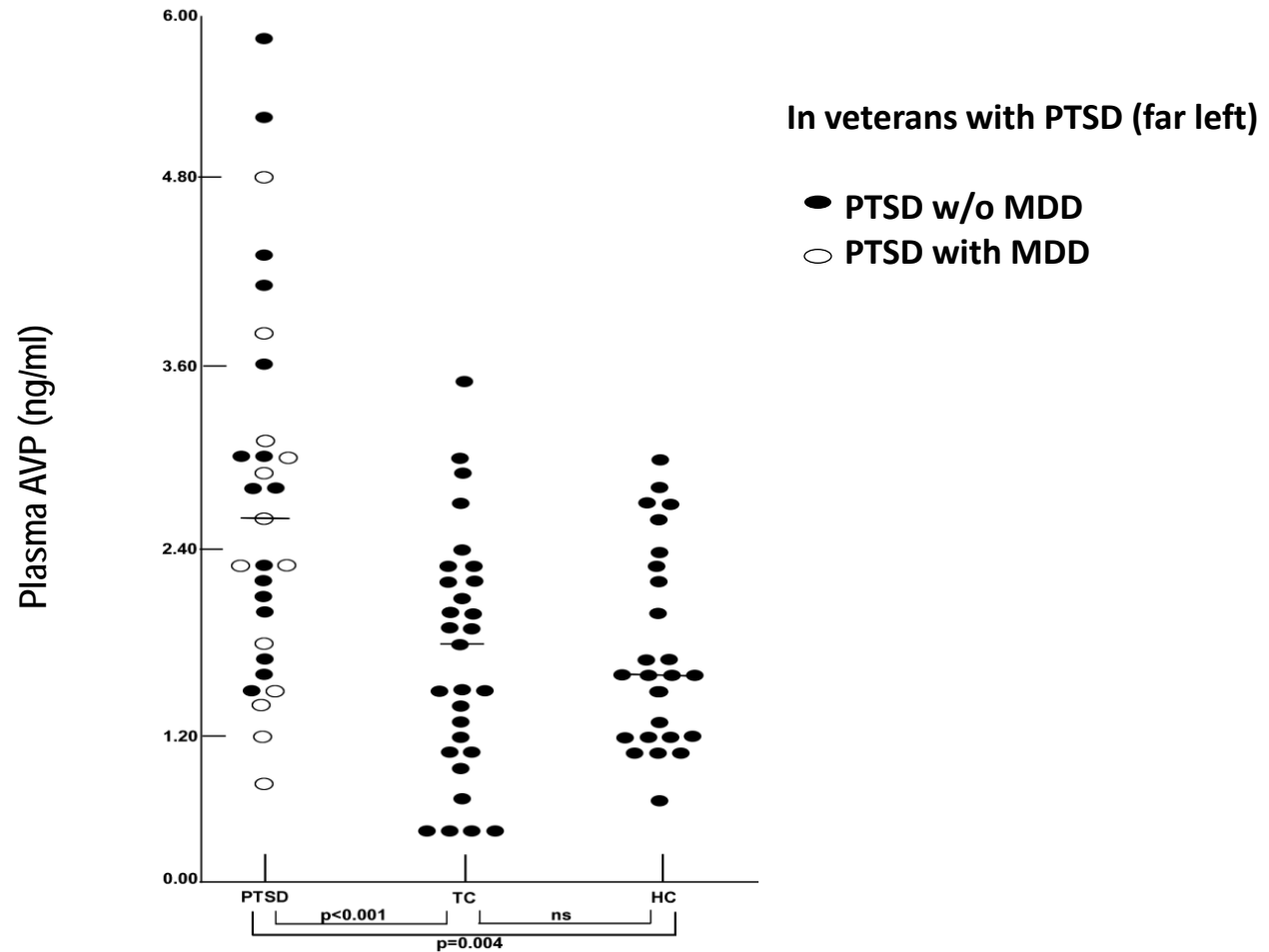
➤ Major Symptoms

- Hyperarousal to Traumatic Memory
- Emotional Dysregulation

➤ Common co-Morbidities

- Major Depression
- Anxiety Disorders
- Impulsivity/Violent Behavior
- Substance Abuse

Plasma AVP is Elevated in Combat Veterans with PTSD



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)

Predatory Conditioned Fear – A Model of PTSD



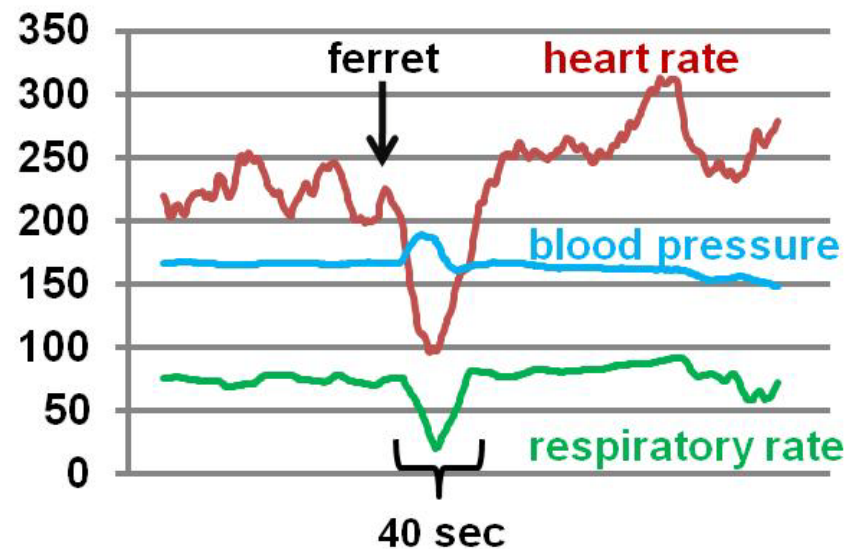
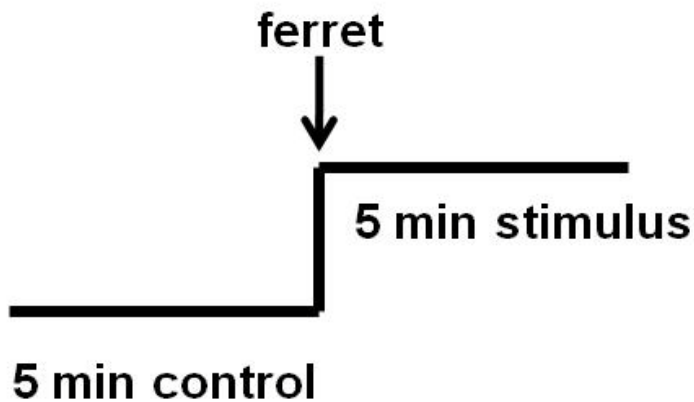
sable ferret



rat

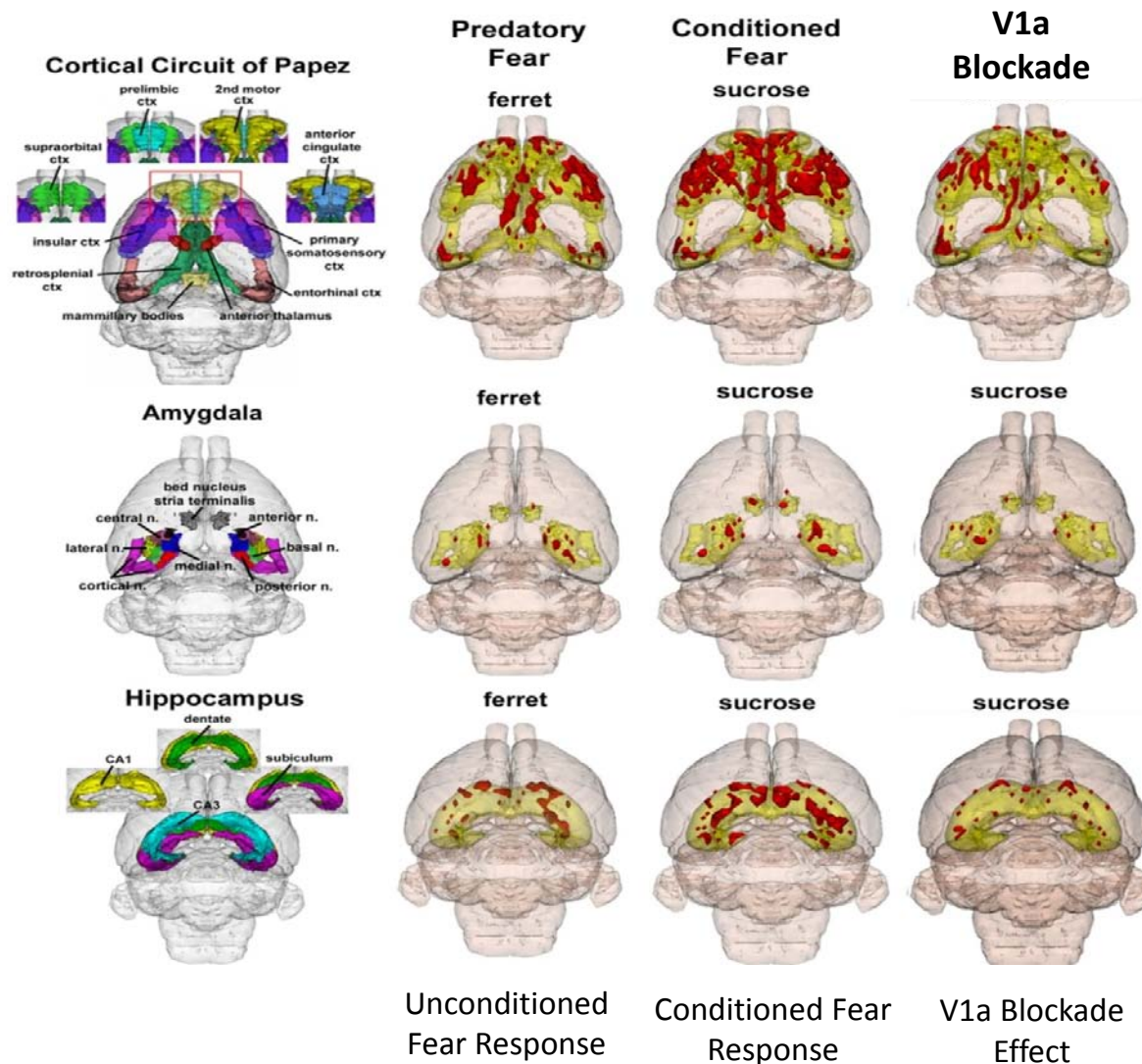
Physiology

Imaging Protocol



Vasopressin Receptor Blockade is Effective in a Conditioned Fear PTSD Model

- V1a receptor block significantly reduced hyperarousal in brain regions mediating fear & memory two weeks after traumatic fear conditioning
- Normal fear responses & arousal patterns were unaffected

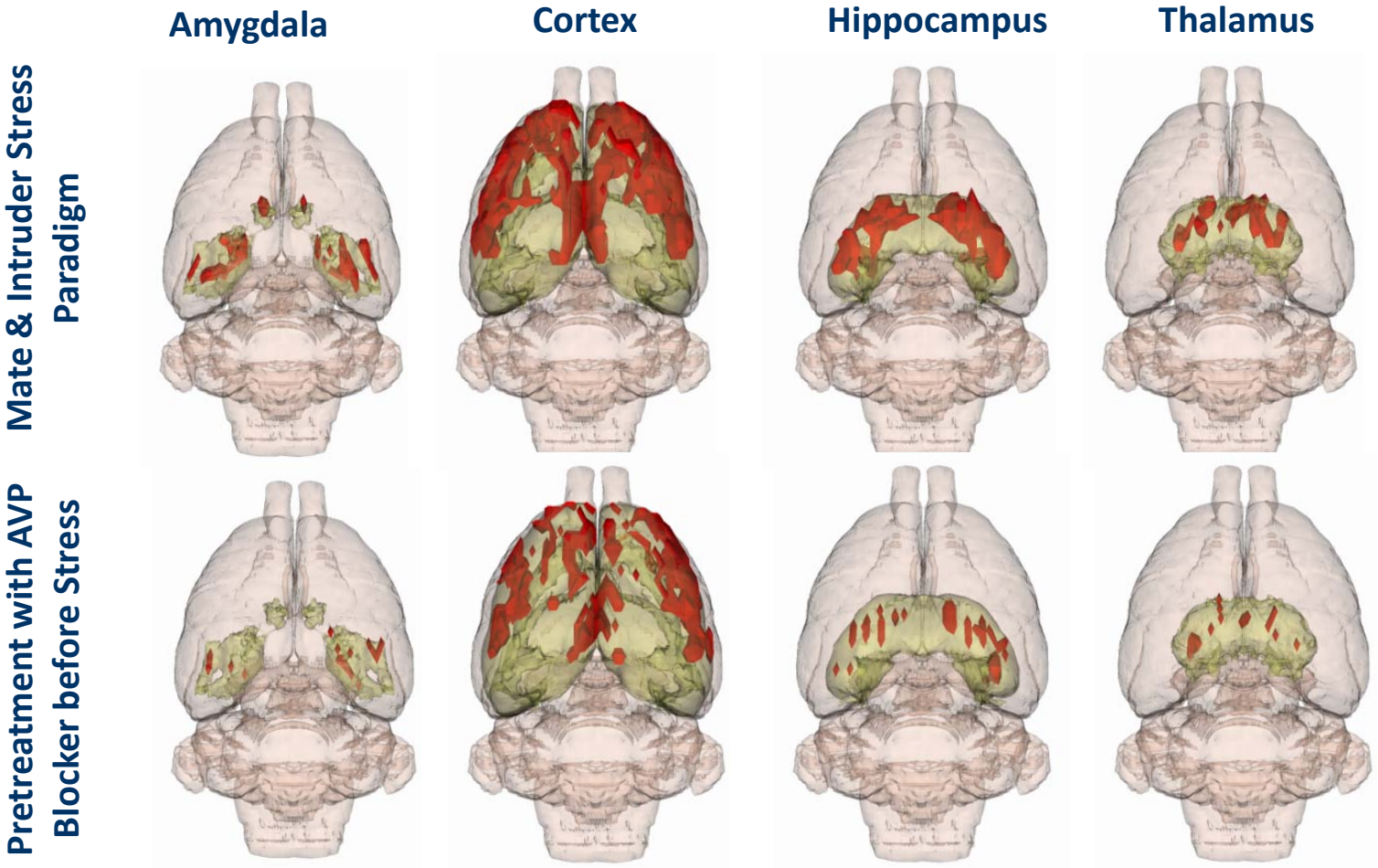


Intermittent Explosive Disorder/Anger Disorders

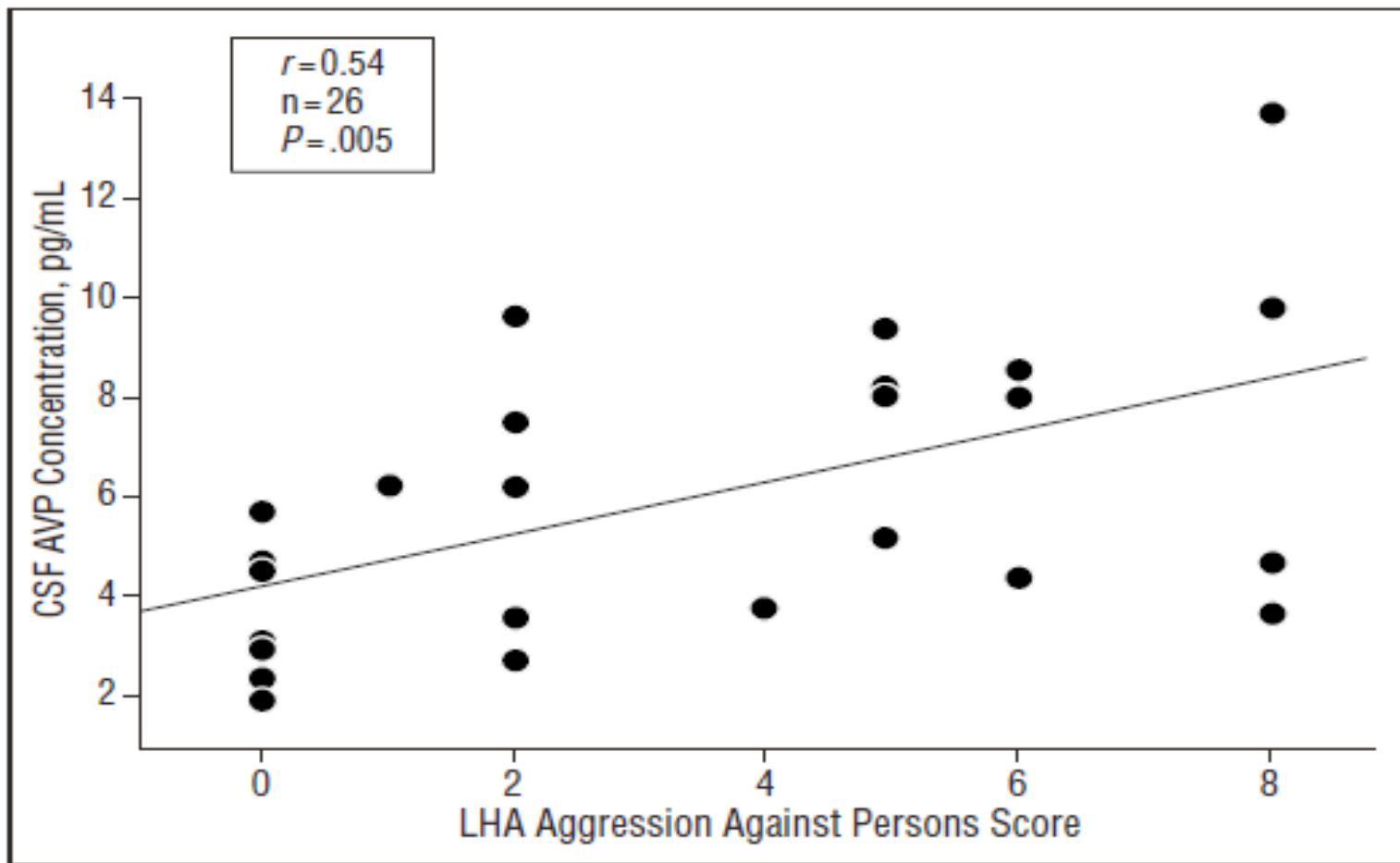
- **Repeated episodes of aggression toward self and/or others**
- **Property Destruction**
- **Explosive Outbursts & Temper Tantrums**
- **Compromised Relationships**
- **Remorse, regret, and guilt**

Vasopressin Blockade: Neuroimaging in Major Brain Regions Linked to Stress-related Disorders

- AVP Blockade attenuates arousal, stress, fear, and aggressive motivation
- Sexual motivation and performance remain intact



CSF AVP is Correlated with Fighting & Assault Scores

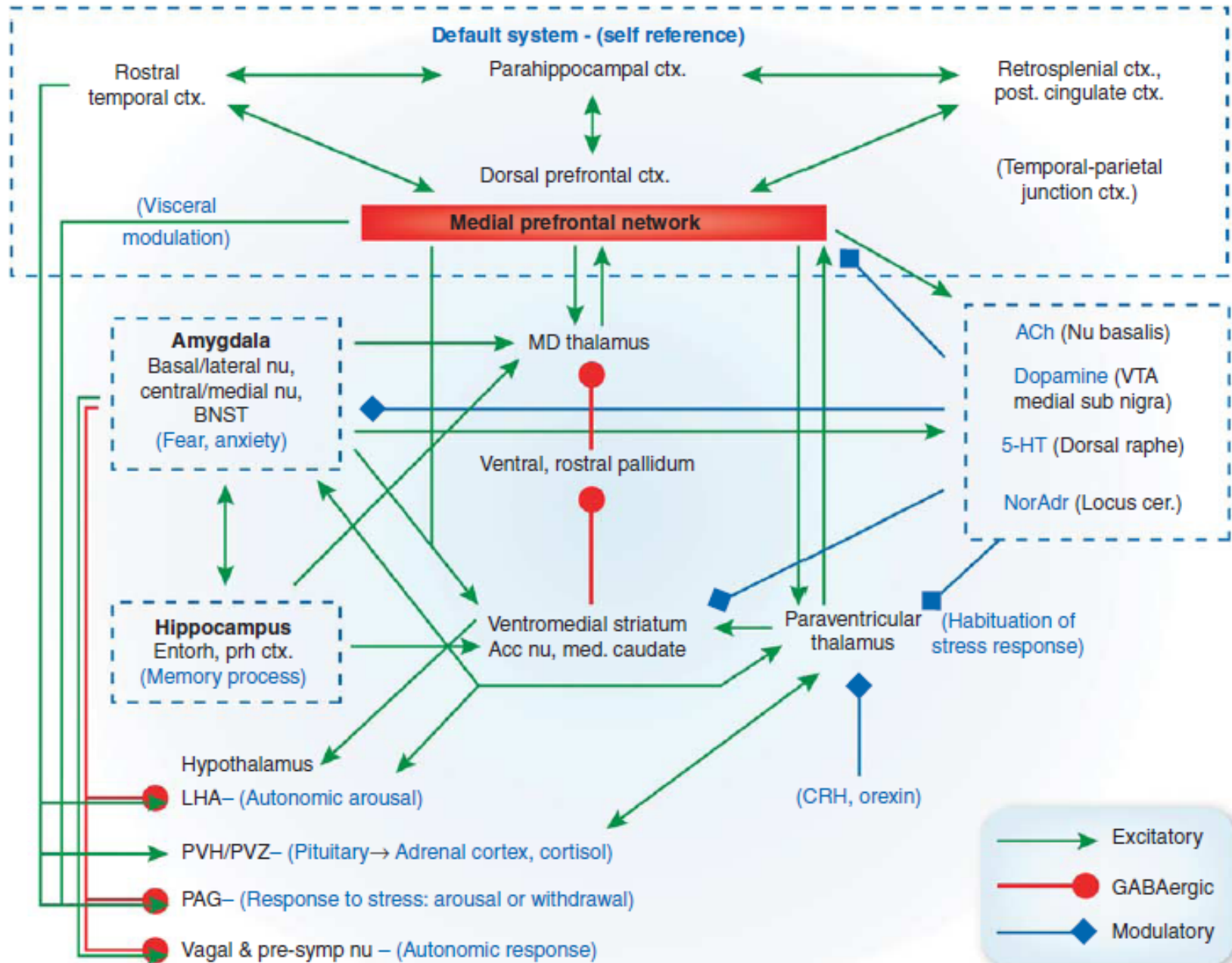


Correlation between Aggression Against Persons (the fighting and assault items) scores on the Life History of Aggression (LHA) assessment and cerebrospinal fluid (CSF) arginine vasopressin (AVP) concentrations in 26 individuals who met the DSM-IV criteria for personality disorder.

Summary: Peptides & Stress-related Disorders

- **CNS AVP receptors are implicated in stress-related disorders through preclinical models & human results**
- **Human studies suggest the involvement of the vasopressin system**
- **Disease-specific circuitry remains to be characterized**
- **Social Neurobiology can potentially identify new pathways for intervention**

Mood Disorders: Medial Prefrontal Network & Amygdala



Alzheimer's Disease

Clinical & Biomarker Changes in Dominantly Inherited Alzheimer's Disease

- **Autosomal Dominant Alzheimer's Disease**
- **Amyloid Hypothesis: 3 genes can cause altered processing (APP, PSEN1, PSEN2)**
- **Compared Carriers & Non-Carriers (n =128)**
- **Clinical, Cognitive, Imaging, & Biochemical Assessments**
- **Normalized against parental age of onset**
- **Follows ADNI protocols and standards**

Clinical & Biomarker Changes in DIAN: Study Measures

- **Clinical: Clinical Dementia Rating Scale (0 – 1)**
- **Neuropsychological: Mini-Mental State Exam (0 – 30) & Wechsler Memory Scale (0 - 25)**
- **Imaging: MRI (volumetric) & PET (metabolism & A β deposition)**
- **Biochemical: CSF & Blood: A β ₁₋₄₂, tau, total tau**

Clinical & Biomarker Changes in DIAN: Results

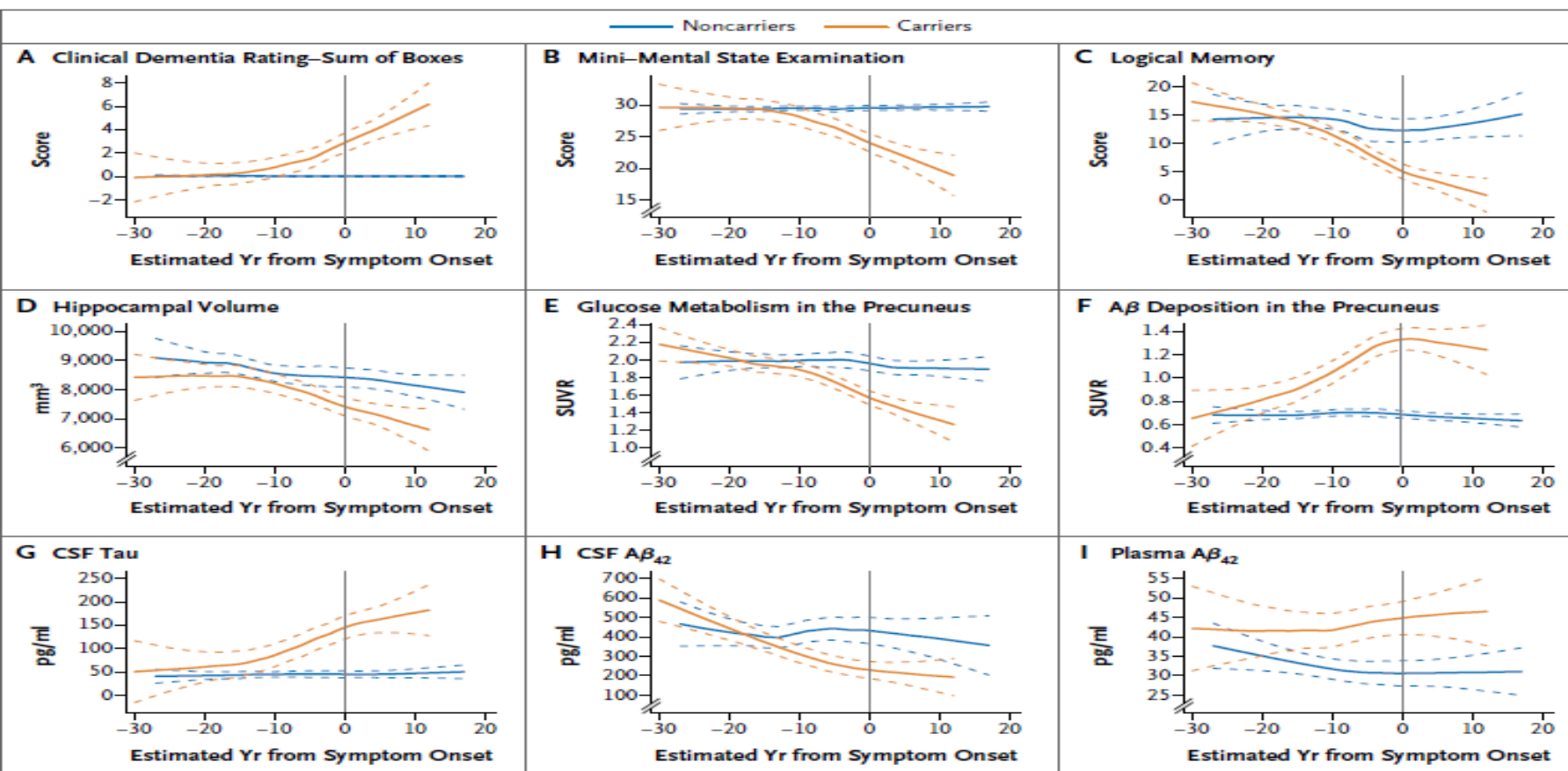


Figure 1. Cross-Sectional Analyses of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes in Autosomal Dominant Alzheimer's Disease Mutation Carriers versus Noncarriers, According to Estimated Years from Expected Symptom Onset.

The clinical and cognitive measures of the Clinical Dementia Rating–Sum of Boxes (scores range from 0 [cognitive normality] to 18 [maximal cognitive impairment]) (Panel A), the Mini–Mental State Examination (scores range from 0 [severe impairment] to 30 [no impairment]) (Panel B), and the Logical Memory subtest of the Wechsler Memory Scale–Revised (scores range from 0 [no recall] to 25 [complete recall]) (Panel C) showed impaired ratings beginning approximately 5 to 10 years before expected symptom onset. MRI measures of hippocampal volume (Panel D) showed increased brain atrophy approximately 15 years before expected symptom onset. Decreases in cerebral glucose metabolism, as measured by positron-emission tomography (PET) with the use of fluorodeoxyglucose (Panel E), occurred approximately 10 years before expected symptom onset, and deposition of amyloid-beta ($A\beta$) in the precuneus, as measured by PET with the use of Pittsburgh compound B (Panel F), began approximately 15 to 20 years before expected symptom onset. In the cerebrospinal fluid (CSF), levels of tau protein (Panel G) increased beginning 10 to 15 years before expected symptom onset, and levels of $A\beta_{42}$ (Panel H) decreased at least 15 years before expected symptom onset. Plasma $A\beta_{42}$ levels were elevated throughout the range of estimated years from expected symptom onset (Panel I). Dashed lines represent 95% confidence intervals of the fitted curves. SUVR denotes standardized uptake value ratio.

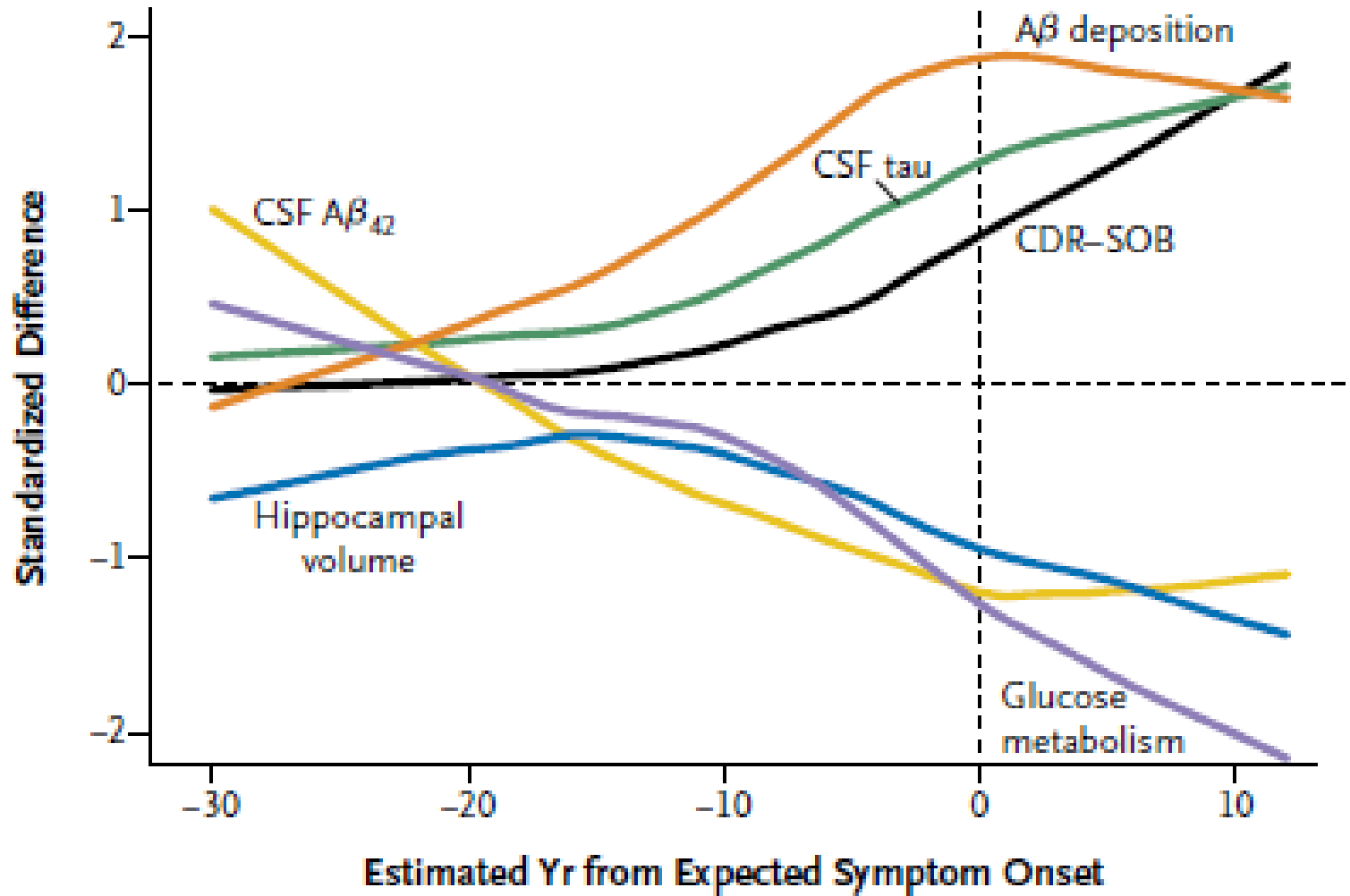
Alzheimer's Biomarkers: Comparison of Clinical Cognitive, Structural, Metabolic, & Biochemical Changes vs. Estimated Expected Years for Symptom Onset

- **Clinical Dementia Rating: + 5 years**
- **Imaging**
 - **MRI: Hippocampal Brain Atrophy + 15 years**
 - **Cerebral Metabolism: +10 years**
 - **Amyloid- β Deposition: + 15 years**
- **Biochemistry**
 - **CSF A β ₁₋₄₂: +20 years**
 - **CSF Tau: + 15 years**



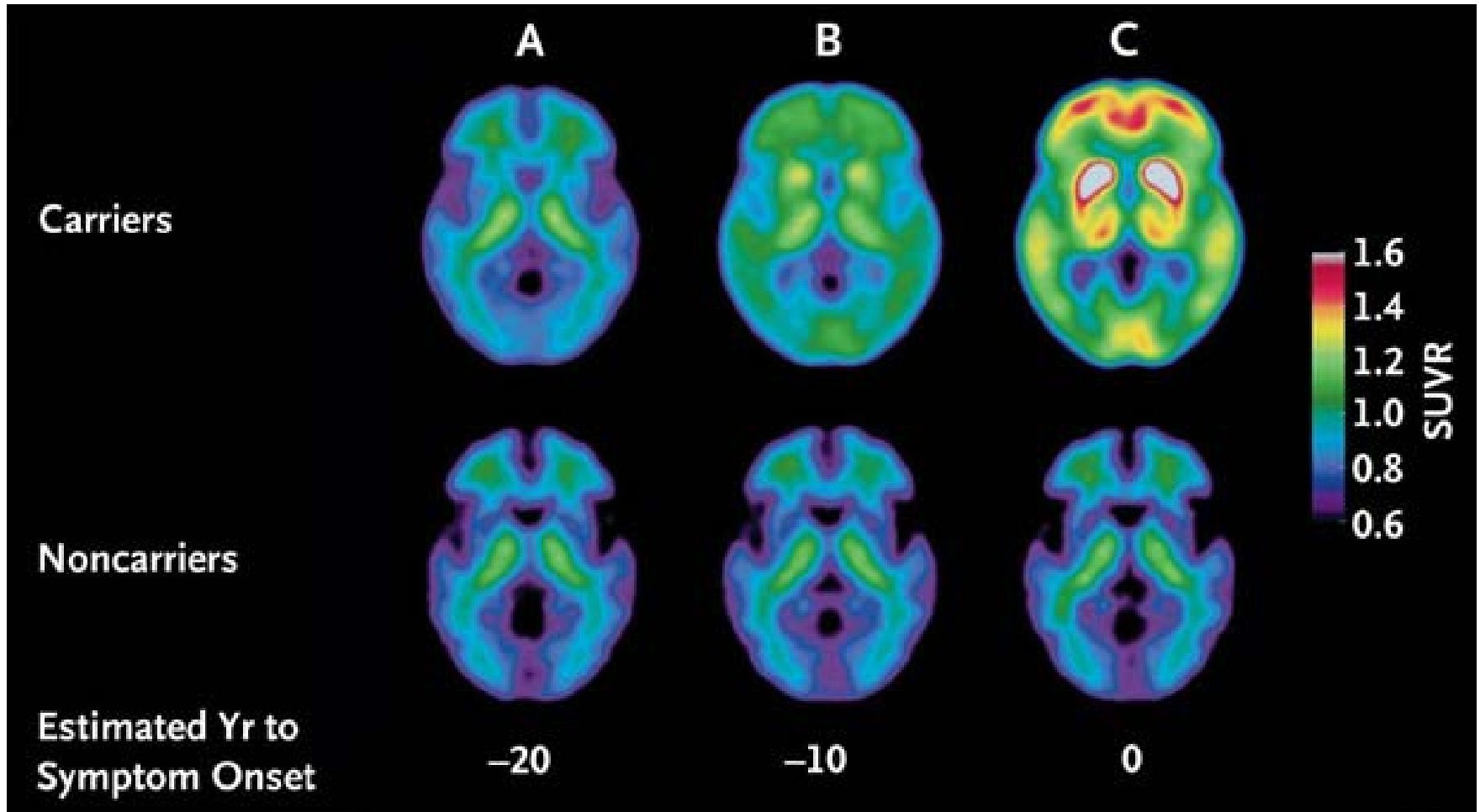
Precuneus

Alzheimer's Biomarkers: Comparison of Clinical Cognitive, Structural, Metabolic, & Biochemical Changes vs. Estimated Expected Years for Symptom Onset



Data shown are differences between mutation carriers and non-carriers

Predicting Alzheimer's Disease: Amyloid- β as a Biomarker



Brain scans show evidence of Alzheimer's disease 20 years before symptoms arise (far left), 10 years before (middle), and after the onset of symptoms (right). Beta amyloid, a protein associated with the disease, is more visible in people who develop the disease (top row) than in those who don't. The more color in the scan, the more beta amyloid is present in the brain.

What Would You Do?

Thank you for your time and attention