Neurobiology of Posttraumatic Stress Disorder

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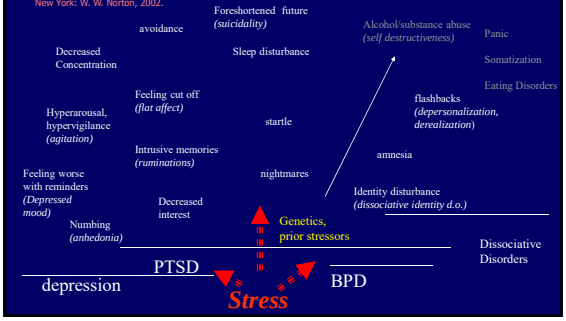
Childhood Abuse-The Invisible Epidemic

- 16% of women have a history of childhood sexual abuse (rape or fondling) based on nationwide surveys (McCauley et al., 1997, JAMA)
- 10% of women (13 million) currently suffer from PTSD (Kessler et al., 1995, AGP), twice as common in women as in men
- Childhood sexual abuse most common cause of PTSD in women

Stress and Psychopathology

Stress may lead to a range of outcomes that do not have validity as discrete constructs
These trauma-related disorders have been termed *Trauma Spectrum Disorders*
From: Bremner JD: *Does Stress Damage the Brain? Understanding Trauma-related Disorders from a Mind-Body Perspective.* New York: W. W. Norton, 2002.



Change In Rank Order Of Disease Burden Worldwide

1990	2020
1. Lower respiratory infection	1. Ischemic heart disease
2. Diarrhea	2. Major depression
3. Perinatal	3. Road traffic accidents
4. Major depression	4. Cerebrovascular
5. Ischemic heart disease	5. COPD
6. Cerebrovascular	8. War
9. Road traffic accidents	12. Violence
16. War	
19. Violence	

Murray and Lopez. *Lancet*. 1997;349:1498.

PTSD: Risk Factors

- Vietnam combat veterans with childhood abuse had 4-fold increased relative risk of PTSD (Bremner et al 1992)
- Most significant factor after adjusting for level of combat exposure, months in Vietnam, participation in atrocities
- Other risk factors: years of education, prior psychiatric illness, young age
- Twin studies: ~12% genetic

How Does the Brain & Body Respond to Stress?

The body has its own in-built alarm system…

How Does the Brain & Body Respond to Stress?

- **Visualization of threat (sight, smell, hearing)**
- **Activation of fear response system – the amygdala**
- **Outpouring of stress hormones →norepinephrine (adrenaline) and cortisol**

How Does the Brain & Body Respond to Stress?

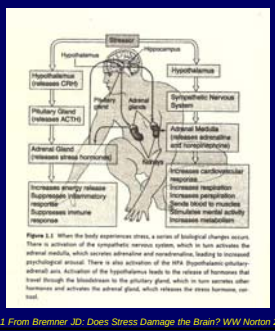
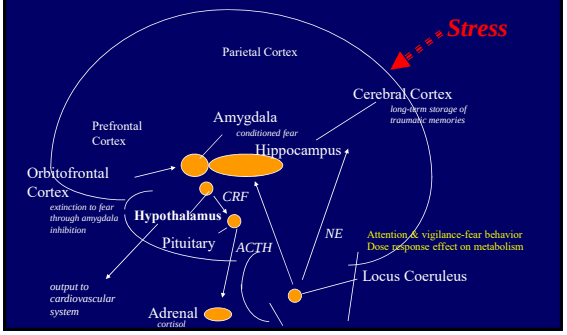


Fig 1.1 From Bremner JD: Does Stress Damage the Brain? WW Norton 2002

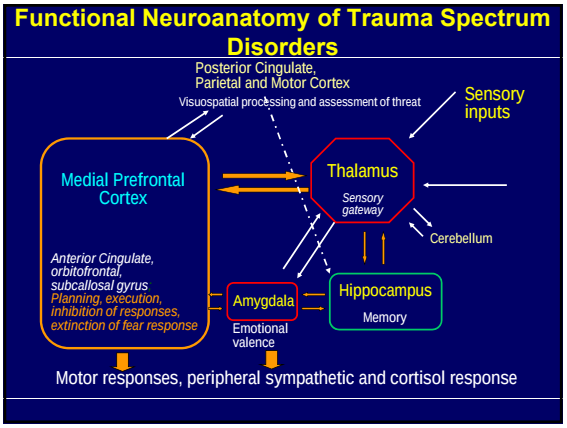
Trauma and Memory

- Trauma associated with a wide range of memory deficits
- Declarative (facts or lists) (hippocampus)
- Nondeclarative (riding a bike, conditioned responses)
- Perseverative errors (frontal)
- Gaps in memory (dissociative amnesia) →relevant to delayed recall of abuse

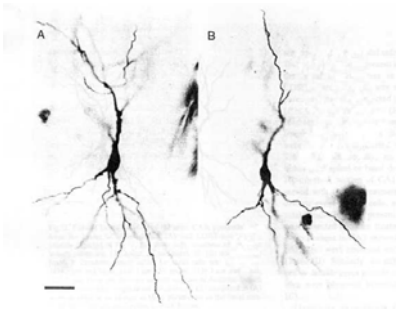
Functional Neuroanatomy of Traumatic Stress



Functional Neuroanatomy of Trauma Spectrum Disorders

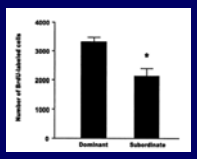


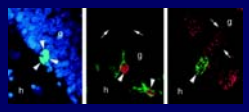
Non-Stressed Stressed



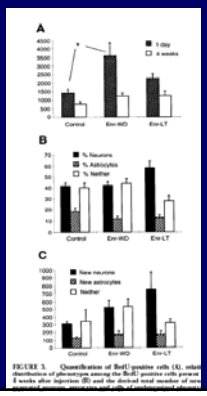
Stress results in decreased dendritic branching of neurons in the CA3 region of the hippocampus (Woolley et al. 1990)

Stress Results in Decreased Hippocampal Neurogenesis





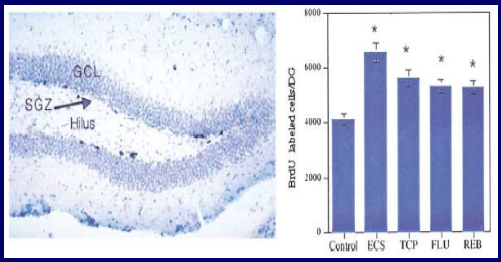
Gould et al 2002



Enriched Environment Promotes Hippocampal Neurogenesis

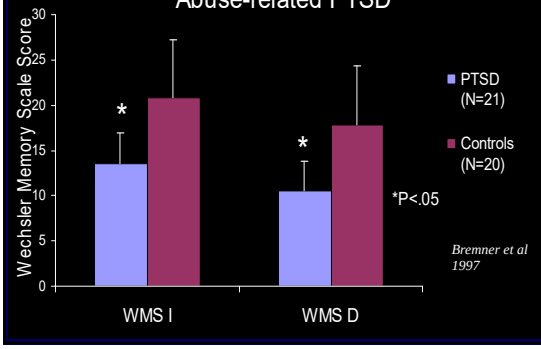
Kempermann et al 99

Antidepressant Treatments Promote Hippocampal Neurogenesis



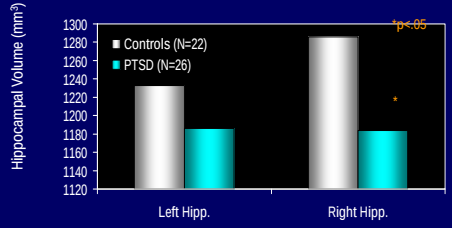
Duman et al 2002

Verbal Memory Deficits in Childhood Abuse-related PTSD

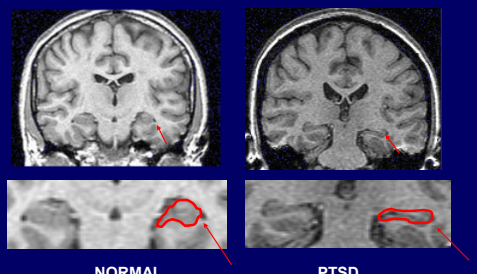


Bremner et al 1997

Decreased Right Hippocampal Volume in Combat-Related PTSD



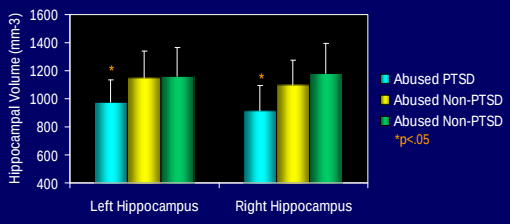
Hippocampal Volume Reduction in PTSD



NORMAL PTSD

J Douglas Bremner, MD, Emory University

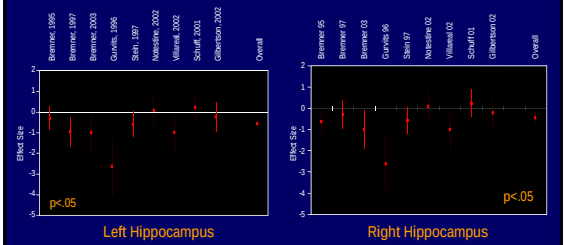
Smaller Hippocampal Volume in Women With Early Childhood Sexual Abuse-Related PTSD



Hippocampal volume measured with Magnetic Resonance Imaging (MRI)
Bremner et al. Unpublished data, 2000.

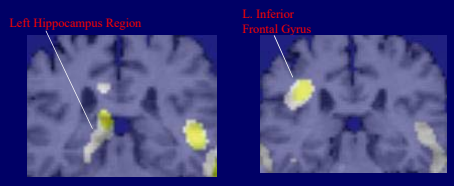
Effect Size Estimates for Hippocampal Volume in Adults With Chronic PTSD vs Healthy Subjects

Pooled Meta-Analysis Demonstrates Smaller Hippocampal Volume in PTSD



Effect size (black square) and 95% confidence interval (red line) measured with Hedges GU.

Failure of Hippocampal Activation in Women with PTSD Related to Childhood Sexual Abuse



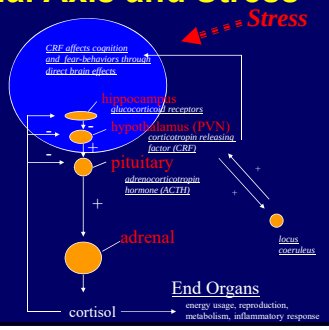
Abused Non-PTSD Women (N=12)

Abused PTSD Women (N=10)

Increased blood flow during encoding of paragraph relative to control condition

Statistical parametric maps overlaid on MR (z score>3.09; p<.001)

Hypothalamic-pituitary-adrenal Axis and Stress



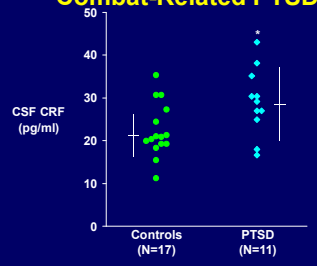
CRF and Stress

- CRF plays an important role in the stress response
- Stress exposure is associated with increases in CRF
- Central CRF administration is associated with fear related behaviors (decreased exploration, increased startle, decreased grooming)

Effects of Stress on HPAA and Hippocampus-Preclinical Studies

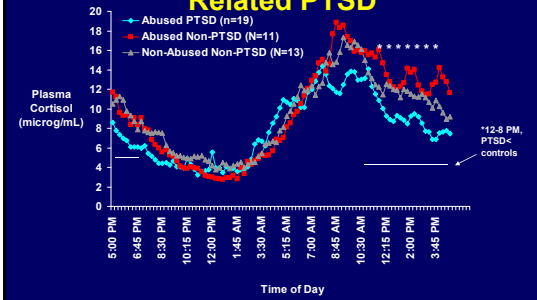
- Stress-induced lesions of the hippocampus result in a removal of inhibition of CRF release from the hypothalamus
- Increased CRF
- Blunted ACTH response to CRF challenge
- Increased Cortisol in the periphery
- Resistance to negative feedback of dexamethasone

Elevated CSF Concentrations Of Corticotropin Releasing Factor In Combat-Related PTSD



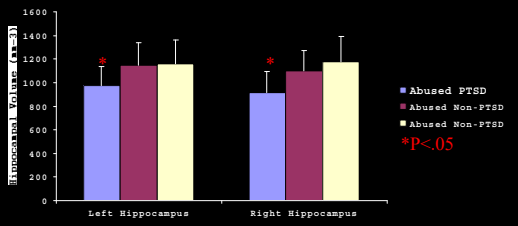
*$P<.05$.
Bremner et al. *Am J Psychiatry*. 1997;154:624-629.

Diurnal Cortisol Levels In Women With Childhood Sexual Abuse-Related PTSD



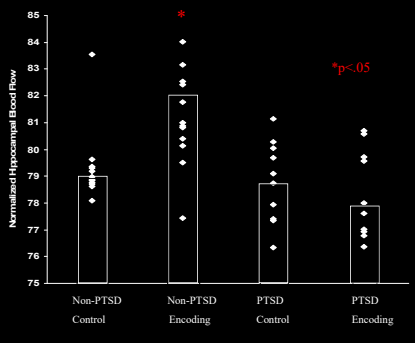
Bremner et al. JNMD 2007

Smaller Hippocampal Volume in Women with Early Childhood Sexual Abuse-related PTSD



Hippocampal Volume measured with Magnetic Resonance Imaging (MRI)
Bremner et al Am J Psychiatry 2003

Failure of Hippocampal Activation with Memory Encoding in Women with Abuse-related PTSD



Conditioned Fear in PTSD

- Pairing of light and shock leads to increased fear responding and increased startle to light alone (conditioned fear)
- Conditioned fear and startle response mediated by central nucleus of the amygdala
- Failure of extinction with lesions of medial prefrontal cortex (inhibits amygdala)
- Study design– habituation (blue square), fear acquisition (blue square + shock), extinction (blue square); control day– random shocks

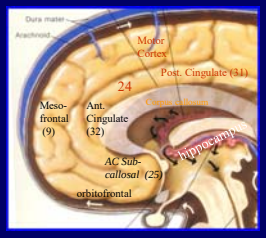
Failure of Extinction in PTSD

- Pairing of light and shock leads to fear responses to light alone
- With exposure to light alone there is a gradual decrease in fear responding ("extinction to fear")
- Reexposure to light-shock at later time point results in rapid return of fear responding
- Medial prefrontal cortical inhibition of amygdala represents neural mechanism of extinction to fear responding
- This brain area mediates emotion (Phineas Gage)

Role of the Medial Prefrontal Cortex in Emotion

- Phineas Gage-19th century-railroad spike entered through his eye socket and lesioned medial prefrontal cortex
- areas involved: orbitofrontal, anterior cingulate (25/24/32), mesofrontal (9)
- Speech and cognition intact
- Marked deficits in ability to judge social contexts, behave appropriately in social contexts, assess emotional nonverbal signals from others

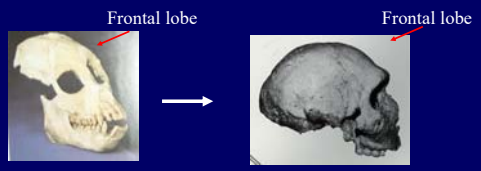
Medial Prefrontal Cortex in Stress & Emotion



- Orbitofrontal Cortex
- Gyrus rectus and medial orbitofrontal cortex
- Anterior Cingulate
- Subcallosal gyrus (area 25) mediates peripheral cortisol and sympathetic responses to stress
- Area 32 implicated in "normal emotion", as well as attention/selection of action (Stroop)
- Anteromesal Prefrontal Cortex
- Superior & Middle Frontal Gyrus (9)

Human Skull Size Makes More Room for the Brain with Time

More skull space means more room for frontal cortex

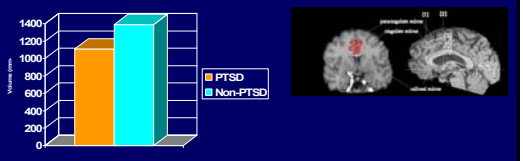


Homo erectus Homo sapiens

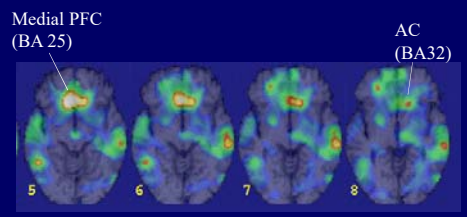
Trauma and the Medial Prefrontal Cortex

- Medial prefrontal cortex involved in inhibition of fear responses in the amygdala (Quirk)
- Early stress associated with decreased dendritic branching in medial prefrontal cortex (Radley)
- Neurological damage associated with deficits in emotional responding (includes orbitofrontal cortex and anterior cingulate)

Decreased Anterior Cingulate Volume in Women with Abuse Related PTSD

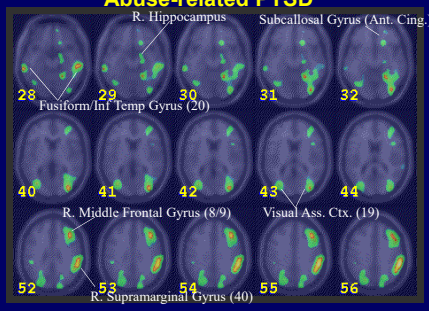


Medial Prefrontal Cortical Dysfunction with Traumatic Memories in PTSD



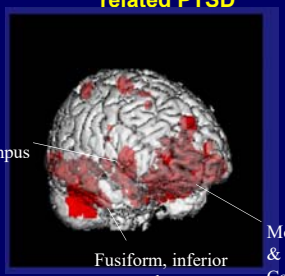
Decreased function in medial prefrontal cortical areas
Anterior Cingulate BA 25, BA 32 in veterans with PTSD compared to
Veterans without PTSD during viewing of combat-related slides & sounds
Z score >3.00; p<.001

Decreased Blood Flow during Memories of Abuse in Women with Childhood Sexual Abuse-related PTSD



Areas displayed with z score>3.00; p<.001

Decreased Blood Flow During Recall of Emotionally Valenced Words in Abuse-related PTSD



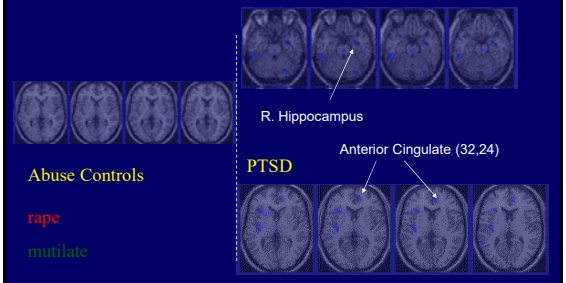
Retrieval of Word pairs like "blood-stench"

Left hippocampus

Medial prefrontal & Orbitofrontal Cortex

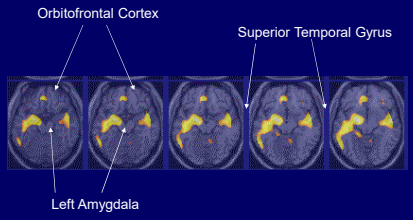
Fusiform, inferior temporal gyrus

Decreased Blood Flow with Emotional Stroop in Abused Women with and without PTSD



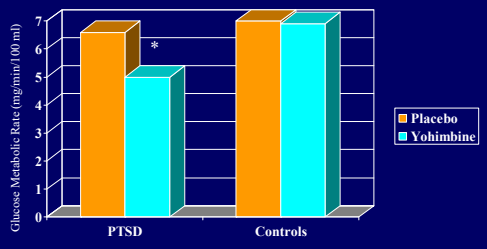
Blue areas represent areas of relatively greater decrease in blood flow, emotional v neutral stroop, z>3.09; p<0.001

Increased Blood Flow with Fear Acquisition versus Control in Abuse-related PTSD



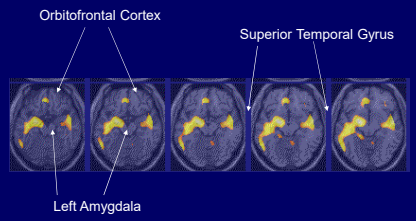
Yellow areas represent areas of relatively greater increase in blood flow with paired vs. unpaired US-CS in PTSD women alone, z>3.09; p<0.001

Decreased Hippocampal Metabolism with Yohimbine in PTSD



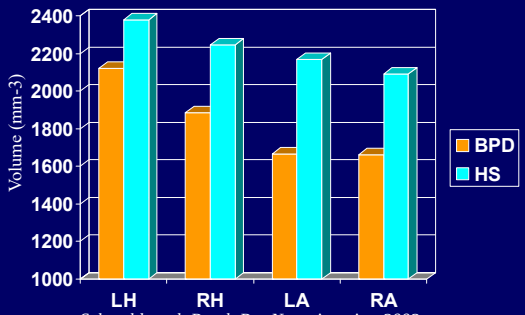
*p<.05, yohimbine versus placebo in PTSD

Increased Blood Flow with Fear Acquisition versus Control in Abuse-related PTSD



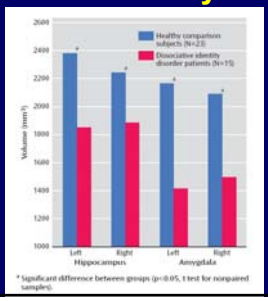
Yellow areas represent areas of relatively greater increase in blood flow with paired vs. unpaired US-CS in PTSD women alone, z>3.09; p<0.001

Smaller Hippocampal and Amygdala Volume in Abused Women with BPD

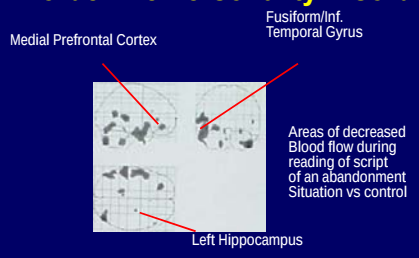


Schmahl et al. Psych Res Neuroimaging 2002

Smaller Hippocampal Volume in Abused Women with Dissociative Identity Disorder

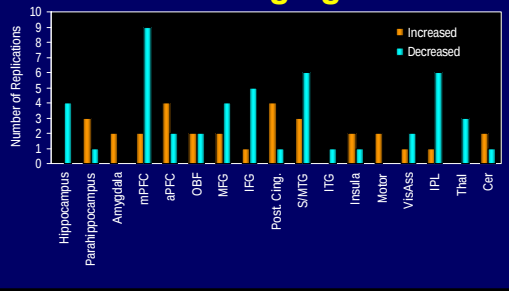


Neural Correlates of Memories of Abandonment in Borderline Personality Disorder



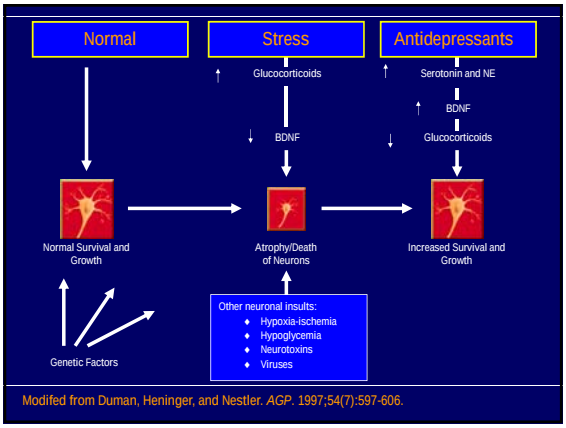
Schmahl et al. *Biol Psychiatry.* **2003; 54:142-151.**

Replications of Findings from Functional Imaging in PTSD



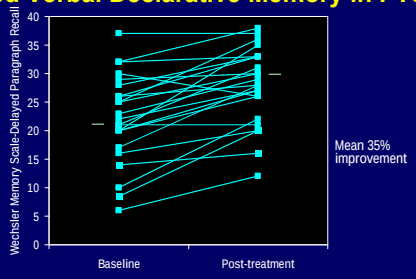
Neural Circuits in PTSD

- Decreased anterior cingulate/medial prefrontal cortex function replicated finding in PTSD
- Other areas: decreased function in hippocampus
- Increased amygdala with fear



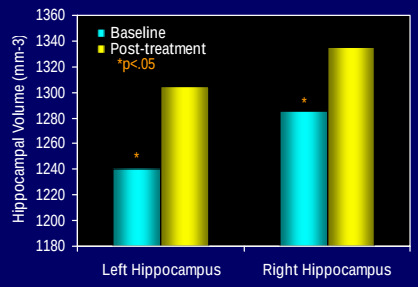
Modifed from Duman, Heninger, and Nestler. *AGP*. 1997;54(7):597-606.

Effects of Paroxetine on Hippocampal-Based Verbal Declarative Memory in PTSD



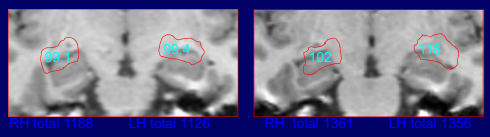
Effects of 9-12 months of treatment with 10-40 mg paroxetine.
Vermetten et al. *Biol Psychiatry*. 2003.

Increased Hippocampal Volume With Paxil in PTSD



Effects of 9-12 months of treatment with 10-40 mg paroxetine.
Vermetten et al. *Biol Psychiatry*. 2003.

Comparison of MRI before and after 9 Months Treatment with paroxetine



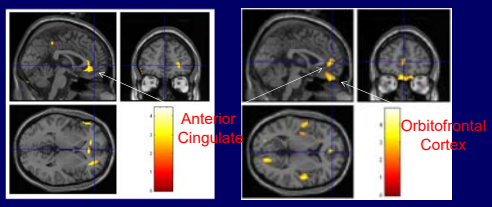
pretreatment posttreatment

Vermetten and Bremner, Biol Psychiatry 2003

Neural Correlates of Antidepressant Treatment of PTSD

- Subjects with PTSD related to sexual or physical abuse or assault
- All subjects free of psychotropic medication
- Treated with 10-40 mg of paroxetine or placebo in a double-blind manner for three months
- Exclusions: History of schizophrenia, schizoaffective disorder, or bipolar disorder, neurological disorder, head injury

Effects of Treatment with Paroxetine and Placebo on Brain Function in PTSD



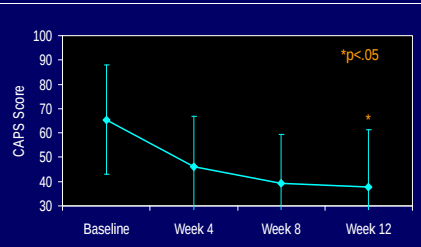
Placebo Paroxetine

Increased function in anterior cingulate with exposure to traumatic scripts after treatment with both placebo and paroxetine. Increased function in orbitofrontal cortex with paroxetine. Fani et al 2011.

Phenytoin and Stress

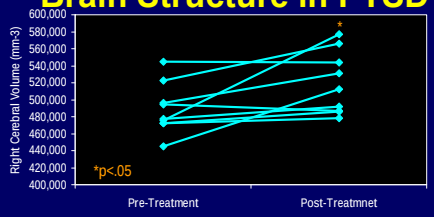
- Phenytoin (dilantin) efficacious in the treatment of epilepsy
- Modulates glutamatergic function
- Blocks the effects of stress on the hippocampus
- Conducted pilot in 9 PTSD subjects

Effect of Phenytoin on Symptoms of PTSD



Nine patients with PTSD from mixed causes treated for 3 months with Phenytoin 300 mg/day on an open label basis.
Bremner et al. 2005 J Clinical Psychiatry

Effects of Phenytoin on Brain Structure in PTSD



- Phenytoin resulted in a significant increase in right brain volume; similar increases in hippocampal volume were seen but not significant after controlling for changes in whole brain volume
- Bremner et al 2005 J Psychopharmacology

Mindfulness Based Stress Reduction (MBSR)

- Mindfulness may be defined as intentionally paying attention to present-moment experience (physical sensations, perceptions, affective states, thoughts and imagery) in a non-judgmental way and thereby cultivating a stable and non-reactive awareness.
- It is a state of sustained attention to these ongoing mental contents and processes without thinking about, comparing, or in other ways evaluating them.

MBSR

- In mindfulness meditation attention is brought to notice whatever thoughts, feelings, and sensations are appearing in awareness, while at the same time remaining aware of the capacity to maintain the focus of attention on these contents, or to deliberately redirect attention to a wider field of awareness or to a different object.

MBSR

- It is suggested that bringing these mental processes under greater voluntary control and directing them in beneficial ways fosters psychological and physical well being, since the patient has a greater sense of control, and thoughts and feelings no longer threaten to overwhelm him/her.

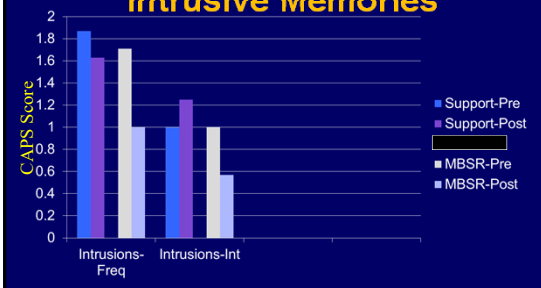
MBSR Treatment of PTSD in Returning Iraq Veterans

- 8-week, 9-session intervention; 2 ½ hour courses each week
- Courses based on learning and refining a range of self-regulatory skills aimed at increasing relaxation and proprioceptive awareness, awareness of mind/body experiences
- Randomized to MBSR or Present Centered Group Therapy (PCGT)

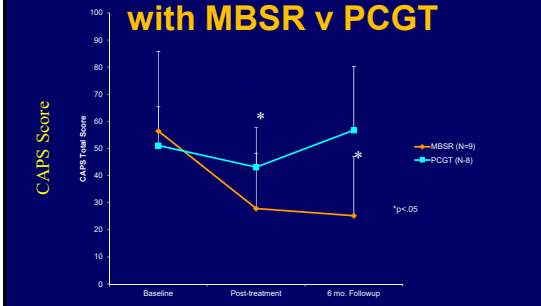
MBSR Treatment of PTSD in Returning Iraq Veterans

- Body scan meditation
- Sitting meditation, focusing on the awareness of breathing, bodily sensations, thoughts, and emotions
- Mindful hatha yoga, stretching and strengthening exercises practiced with awareness of breathing and intended to develop awareness (mindfulness) during movement.
- Guided meditation CDs to be practiced @home

Effects of MBSR on Intrusive Memories

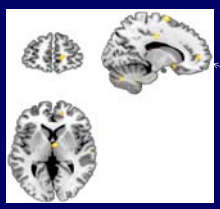


Decreased PTSD Symptoms with MBSR v PCGT



Effects of MBSR on Global Improvement

Effects of Treatment MBSR on Brain Function in PTSD



Increased function in anterior cingulate with MBSR v PCGT

Conclusions

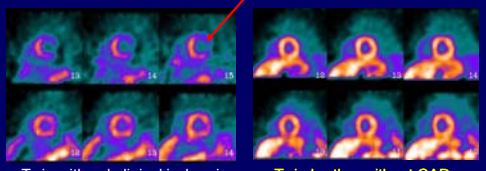
- MBSR safe and effective in returning combat veterans with PTSD
- No complications in PTSD patients with treatment
- Improved PTSD symptoms sustained at six months
- Increased anterior cingulate function with MBSR - neural correlate of brain response to treatment

Positron Emission Tomography (PET) Myocardial Perfusion Imaging

- Noninvasive assessment of subclinical CAD
- Absolute quantitation of coronary blood flow at rest and after pharmacological stress
- Ratio of stress flow to rest flow: coronary flow reserve (CFR)
- Measure of whole coronary circulatory function and vasodilator capacity
- In absence of coronary stenoses, index of microvascular disease

de Silva R, Camici PG, Cardiovasc Res 1994
Kaufmann PG, Camici PG, J Nucl Med 2005

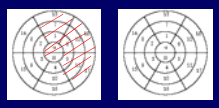
Myocardial Perfusion Scoring in Twins



Twin with subclinical ischemia

Twin brother without CAD

Twins underwent PET imaging after 20 mCi N-13 ammonia injection after rest or adenosine stress



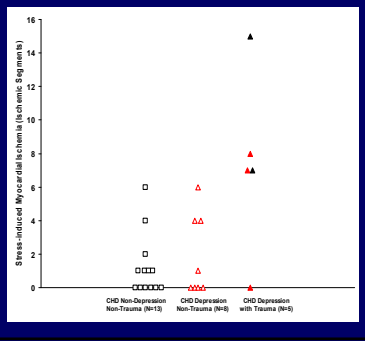
Stress Rest

11 segments with severe ischemia (score of 3 [severe] each)

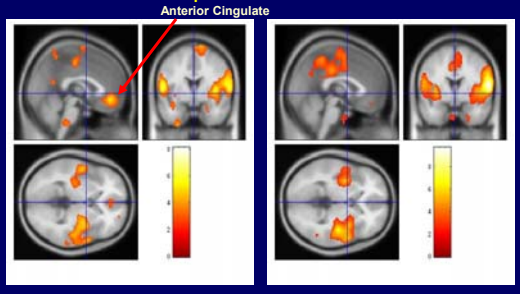
- *total stress severity score=33*
- *rest score=0*
- *difference score=33*

His twin brother had a score of zero.

Increased Stress Induced Myocardial Ischemia in Trauma & Depression



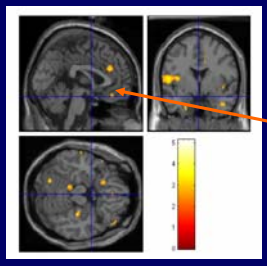
Decreased Anterior Cingulate Function with Stress in Depressed CHD Patients



CHD with Depression

CHD without Depression

Decreased Anterior Cingulate Activation in Patients with CHD and Depression during Stress Induced Myocardial Ischemia



Decreased blood flow in anterior cingulate (arrow) in patients with CHD and depression during stress-induced myocardial ischemia (N=5) relative to patients with CHD and depression without stress-induced myocardial ischemia (N=8). There were also decreases in hippocampus.

Stress, Behavior and Heart Disease: Conclusions

- Brain areas affected by stress involved in PTSD & Depression
- Prefrontal Cortex, amygdala and Hippocampus
- These brain areas mediate effects of stress on myocardial ischemia

Vagal Nerve Stimulation in Psychiatry: Back to the Future

EMORY UNIVERSITY

Georgia Tech

J. Douglas Bremner, MD
Emory U. & Atlanta VA

Omer Inan, PhD
Georgia Tech

Vagal Nerve Stimulation (VNS) in Psychiatry: Rationale

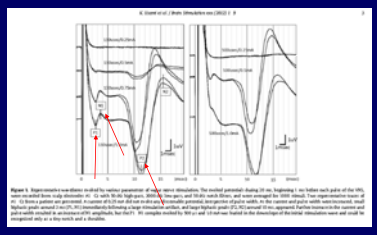
- Depression and disorders related to psychological trauma like posttraumatic stress disorder (PTSD) have a neurobiology likely to benefit from VNS
- Associated with increased amygdala function and inflammation
- VNS can counter these effects, modulate primary neurobiology

Vagal Nerve Stimulation (VNS) for Refractory Depression

- Implantable VNS FDA-approved approved for treatment refractory depression
- Positive results from several multi-site controlled trials
- 68% clinical response rate and 43% remission (> than treatment as usual)
- Not approved for Medicare payment, limited utility, inconvenience of surgery

Aaronson et al "5 year observational study of patients with treatment-resistant depression treated with VNS," Am J Psychiatry 2017; 174:640ff.

Non-Invasive VNS: Validation of Vagal Stimulation with Evoked Potentials



P1 N1 P2 evoked potential (EP) (red arrows) signal characteristic of vagal nerve stimulation

Non-Invasive VNS: Back to the Future

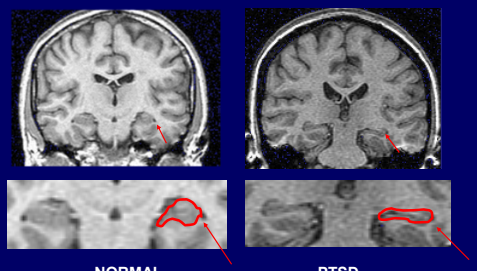
- Non-invasive VNS deliverable via neck stimulation
- FDA approved for cluster headache (only efficacious for intermittent)
- Potential wide-spread applicability for psychiatry due to convenience and cost
- We have approval from Emory IRB for PTSD and traumatized healthy subjects

Bremner & Rapaport, "Vagal nerve stimulation: Back to the Future," Am J Psychiatry 2017; 174:609-611.

Posttraumatic Stress Disorder

- Neural circuitry involves amygdala, hippocampus, prefrontal cortex
- Increased inflammatory and sympathetic activity
- Increased cardiovascular reactivity to stressful reminders
- Associated with increase in cardiovascular disease

Hippocampal Volume Reduction in PTSD

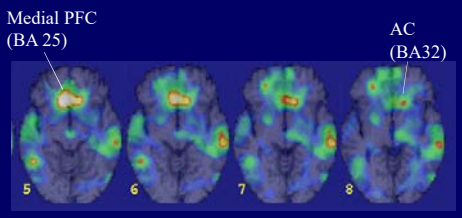


NORMAL PTSD

J Douglas Bremner, MD, Emory University

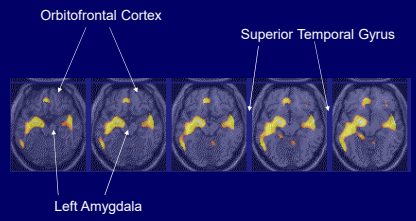
Bremner et al Am J Psychiatry 1995

Medial Prefrontal Cortical Dysfunction with Traumatic Memories in PTSD



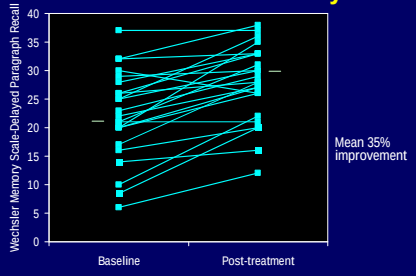
Decreased function in medial prefrontal cortical areas
Anterior Cingulate BA 25, BA 32 in veterans with PTSD compared to Veterans without PTSD during viewing of combat-related slides & sounds
Z score >3.00; p<.001; Bremner et al Biol Psychiatry 1999

Increased Blood Flow with Fear Acquisition versus Control in Abuse-related PTSD



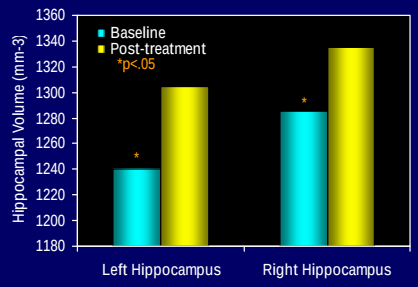
Yellow areas represent areas of relatively greater increase in blood flow with paired vs. unpaired US-CS in PTSD women alone; z>3.09; p<0.001; Bremner et al 2004

Effects of Paroxetine on Hippocampal-Based Verbal Declarative Memory in PTSD



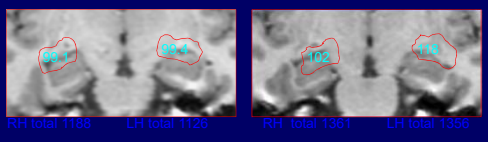
Effects of 9-12 months of treatment with 10-40 mg paroxetine.
Vermetten et al. *Biol Psychiatry*. 2003.

Increased Hippocampal Volume With Paroxetine in PTSD



Effects of 9-12 months of treatment with 10-40 mg paroxetine.
Vermetten et al. *Biol Psychiatry*. 2003.

Comparison of MRI before and after 9 Months Treatment with paroxetine



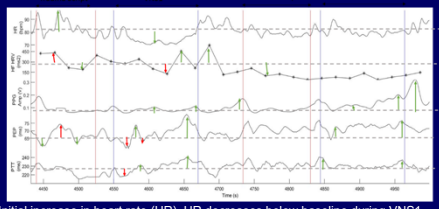
pretreatment posttreatment

Vermetten and Bremner, Biol Psychiatry 2003

Effects of VNS on Cardiovascular Reactivity with Traumatic Scripts

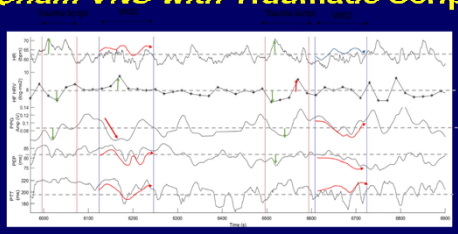
- Healthy human subjects with history of psychological trauma, no PTSD
- Three day protocol with exposure to personalized traumatic scripts and mental stressors (public speaking, arithmetic)
- PET imaging of the brain on day one
- Measurement of inflammatory and other biomarkers with VNS or sham stimulation

Active VNS with Traumatic Scripts



- Initial increase in heart rate (HR). HR decreases below baseline during VNS1.
- VNS2 does not cause the same effect.
- High Frequency Heart Rate Variability (HF HRV) shows first a decrease, then increase, during and after VNS1.
- Photoplethysmography (PPG) amplitude, Pre-Ejection Period (PEP, a marker of sympathetic function) and Pulse Transit Time (PTT) reach higher values than baseline, by the end of VNS1.
- VNS2 only shows an increase in PPG and PEP.

Sham VNS with Traumatic Scripts



- HR, HF HRV and PPG increases during the first traumatic script.
- During VNS1, HR, PEP and PTT fluctuate around baseline, HF HRV increases, PPG decreases then increases.
- For the second traumatic script, similarly, HR, HF HRV, and PTT fluctuate around baseline.
- PPG first decreases, then increases after VNS2, and PEP decreases.
- DARPA TNT & ElectRx Programs Project at Emory/Georgia Tech

VNS Conclusions

- Non-invasive VNS associated with reduction in cardiovascular reactivity to traumatic reminders
- Evidence of decreased sympathetic response to stress
- Implications for application to PTSD and depression for symptom reduction as well as reduction in associated physical disorders

VNS Future Directions

- Study of PTSD patients with stress / biomarker / imaging protocol (recently approved)
- Further map physiology of VNS in health and disease
- Apply as tool for treatment of PTSD using logical biomarkers and neurophysiology to map treatment response