**Dennis S. Charney, MD**
**Dean**
**Icahn School of Medicine at Mount Sinai**

# *"RESILIENCE: THE SCIENCE OF MASTERING LIFE'S GREATEST CHALLENGES"*

## Department of Health Evidence and Policy

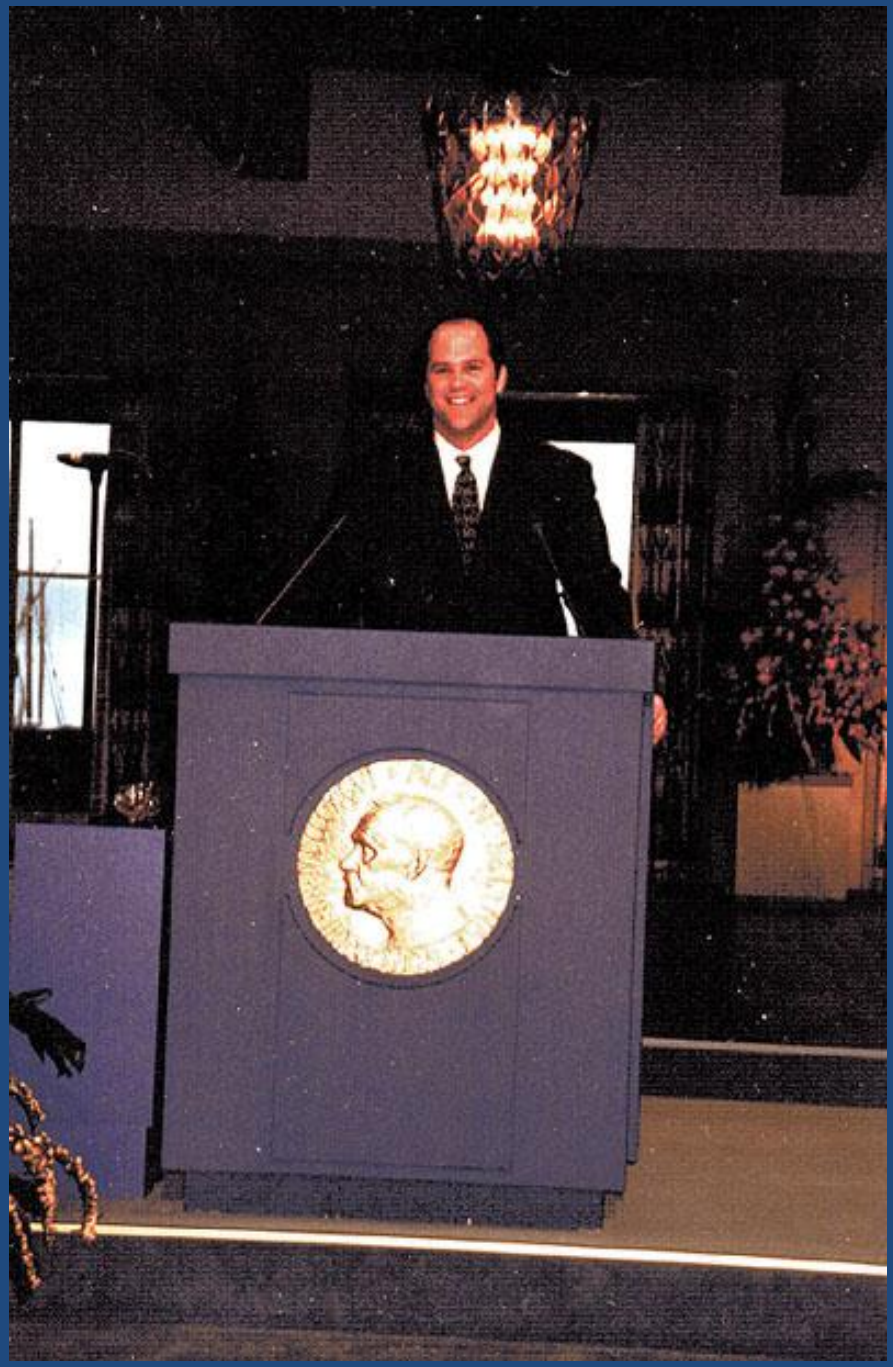
**Grand Rounds**

**Tuesday, April 22, 2014**

Mount Sinai

# WHAT I HOPE YOU TAKE OUT OF THIS LECTURE

1. Psychological Stress Alters Brain Function
2. Psychobiological mechanisms of Human Resilience to Stress
3. You can train to be more Resilient
4. Implications for your own life

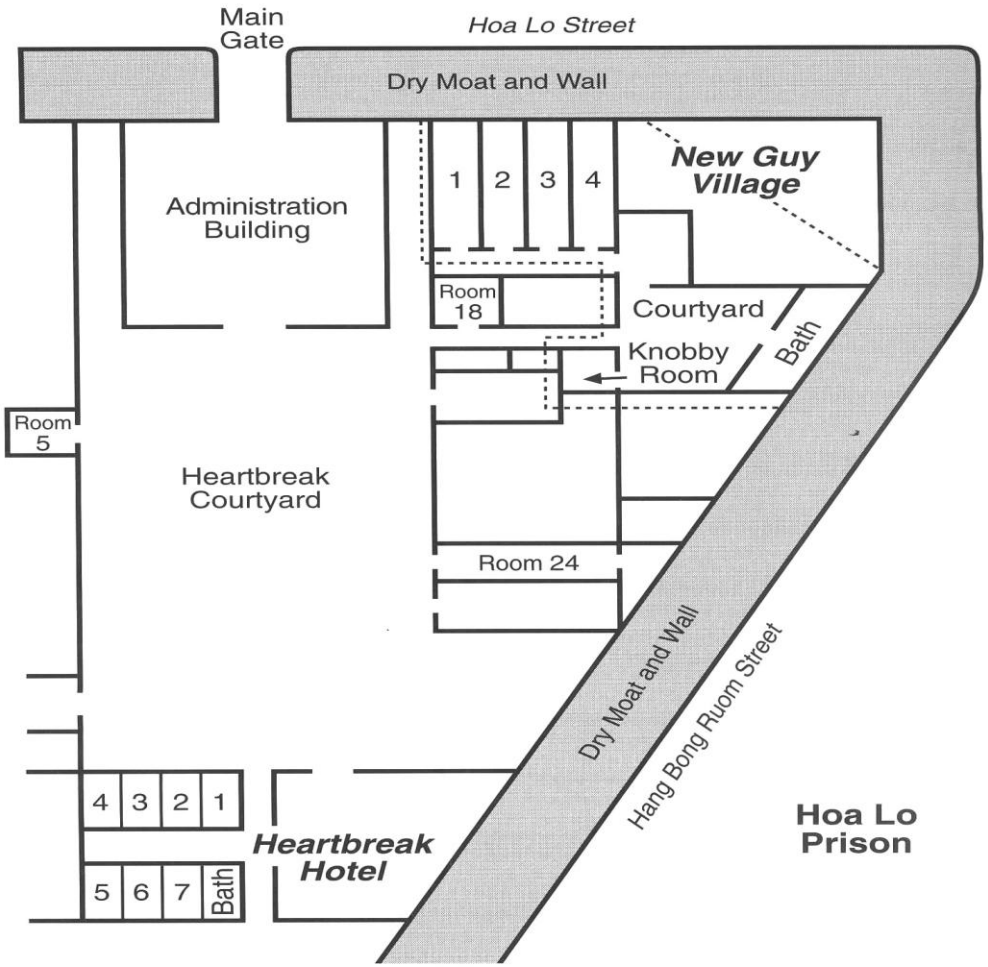



Reebok


Gruen,Deborah
Swimming
Athens 2004

Deborah Gruen, HNHS and Michael Prout, UN
USA Swimming National Disability Championships
2002

# Hanoi Hilton




*Heartbreak Hotel and New Guy Village*

**Rochester & Kiley (1999), Honor Bound: American Prisoners of War in Southeast Asia, 1961-1973**

**John M. McGrath (1975), Prisoner of War:  Six Years in Hanoi**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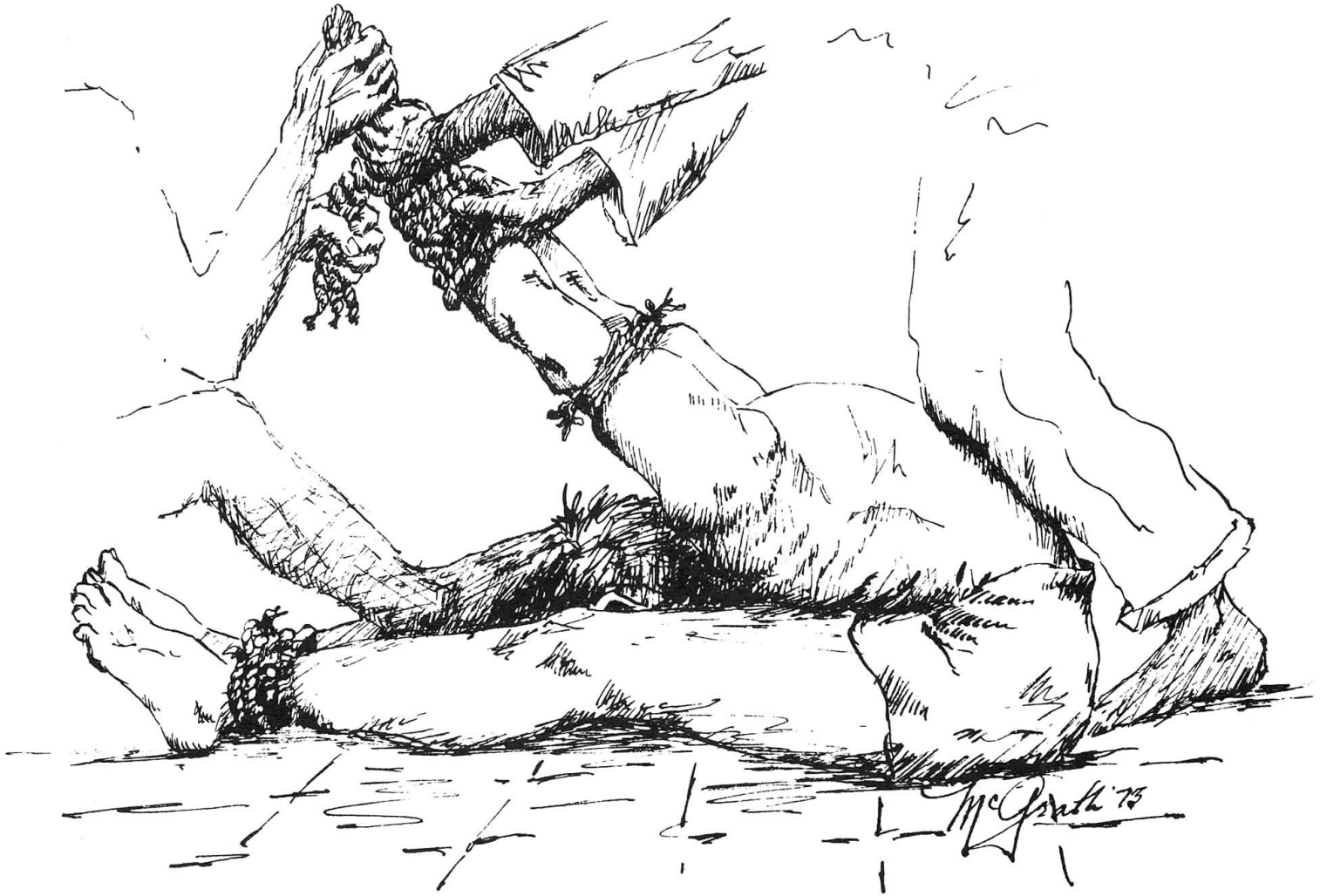


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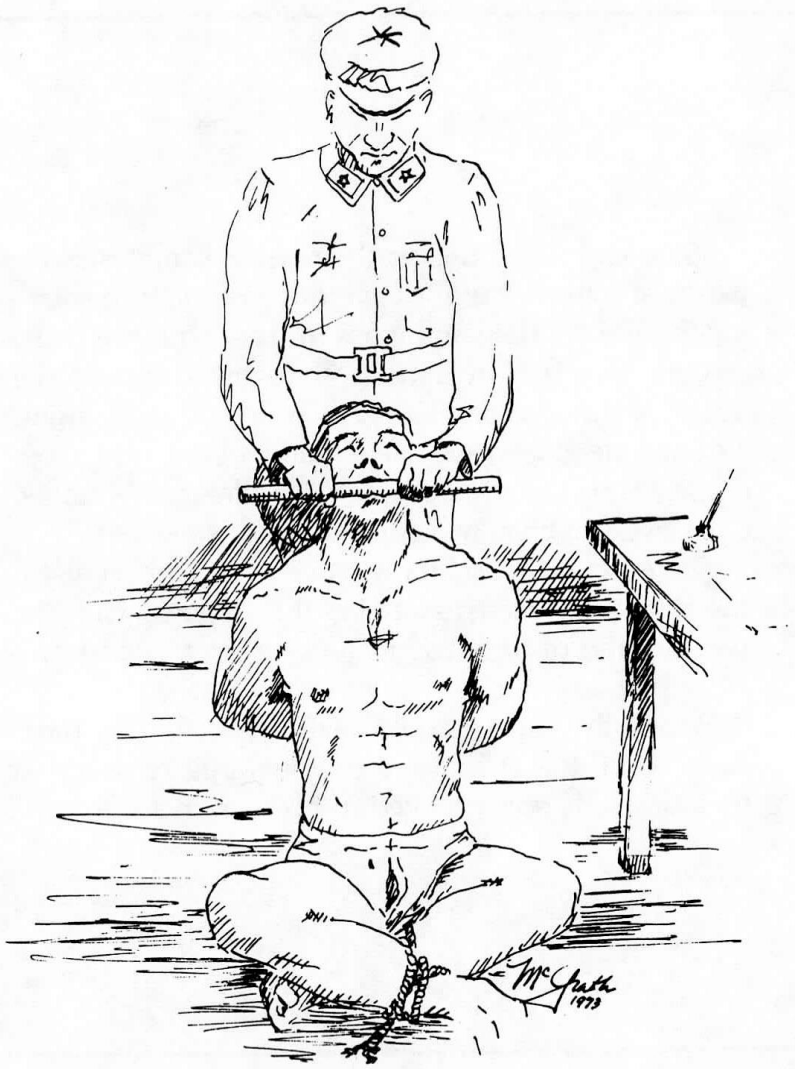

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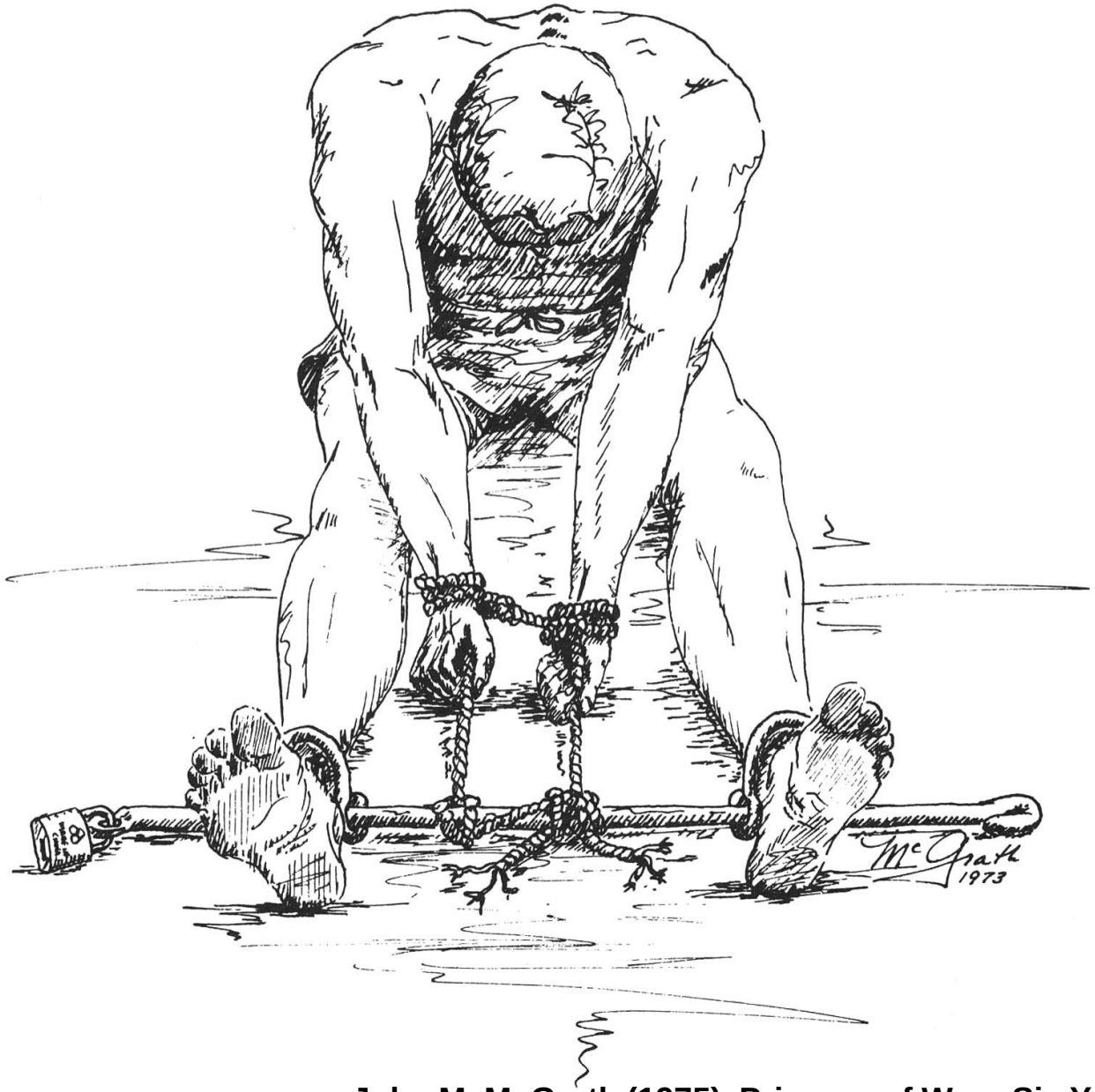


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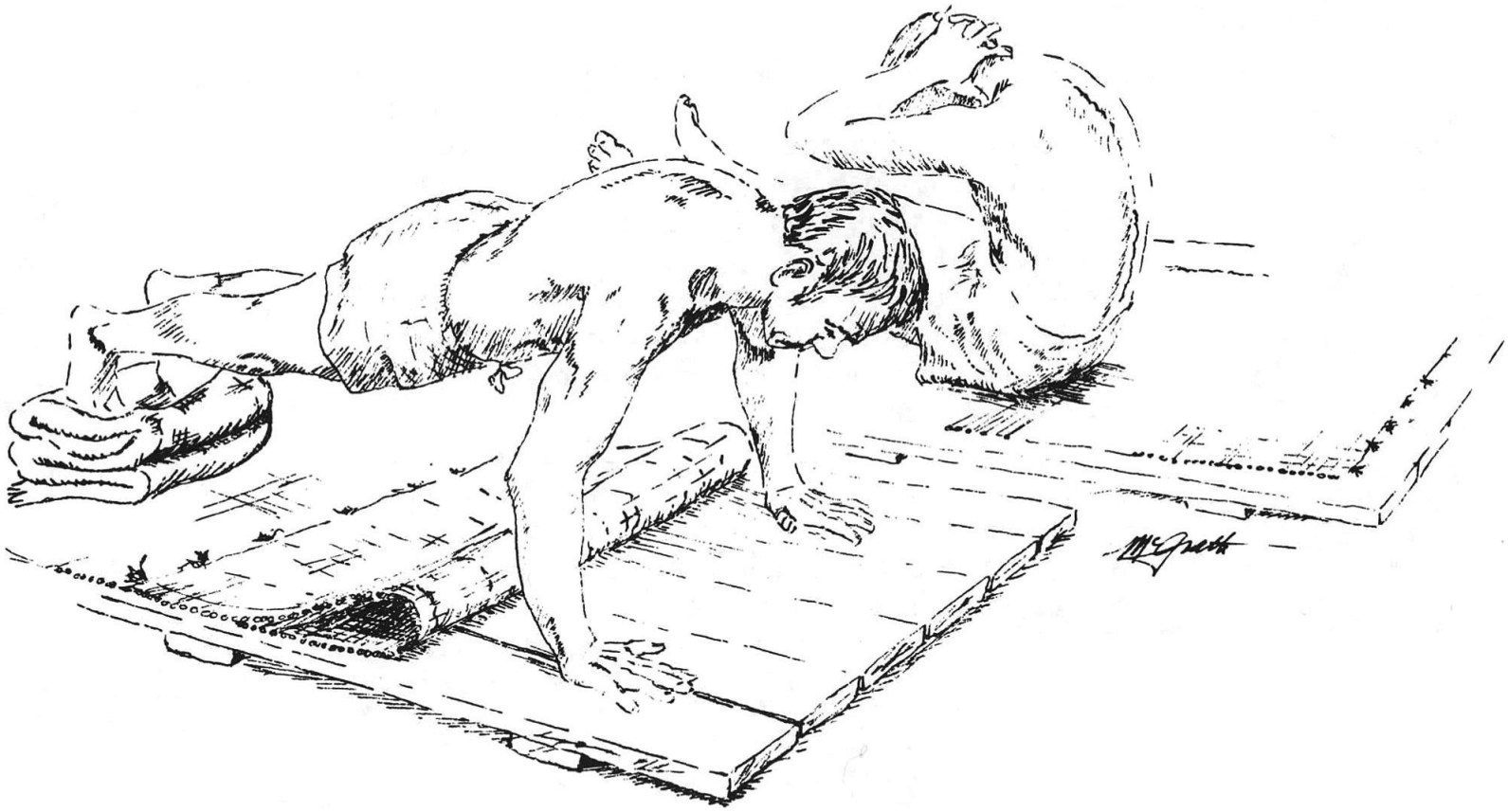
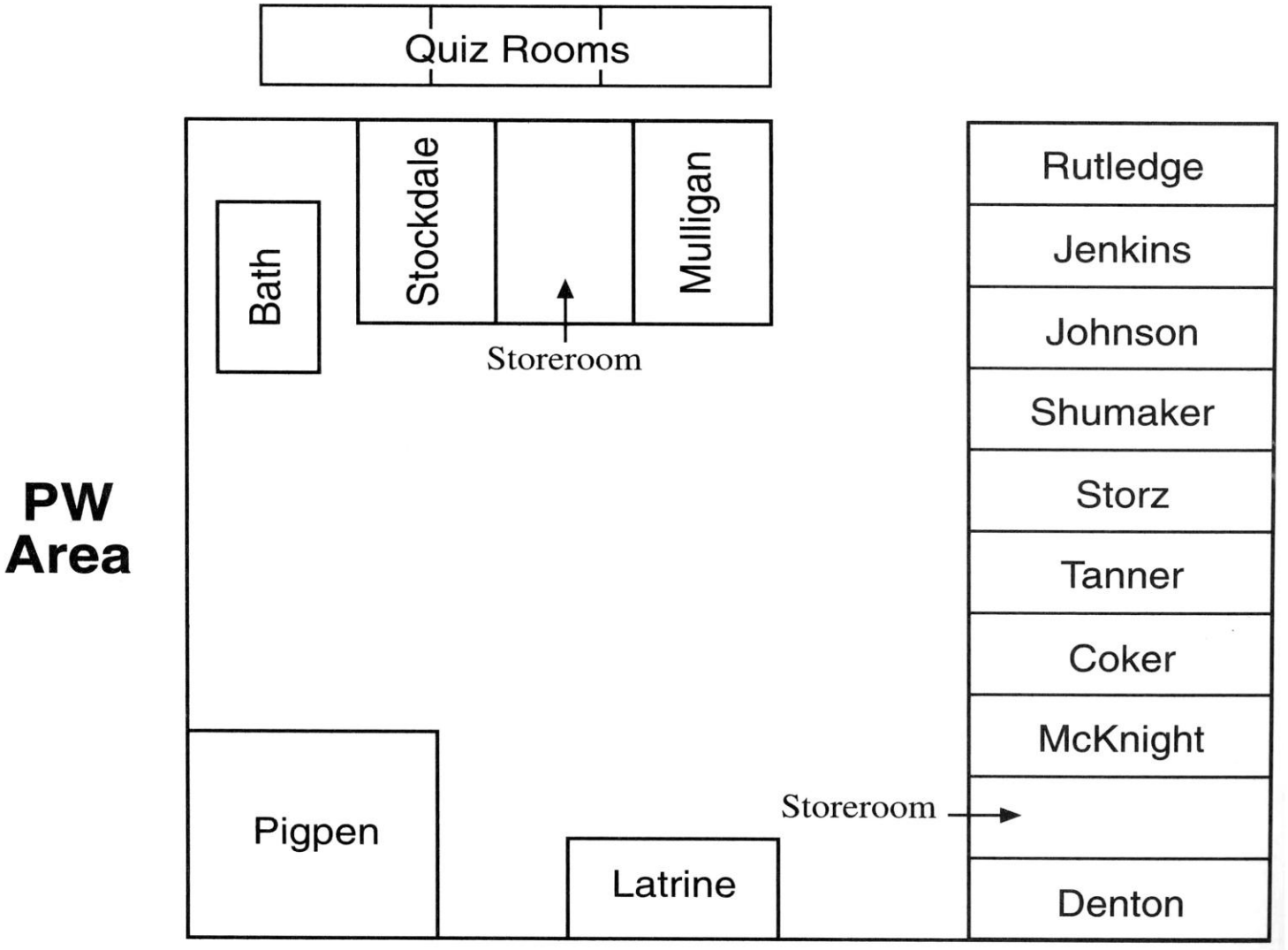
| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1 | A | B | C | D | E |
| 2 | F | G | H | I | J |
| 3 | L | M | N | O | P |
| 4 | Q | R | S | T | U |
| 5 | V | W | X | Y | Z |



**John M. McGrath (1975), Prisoner of War:  Six Years in Hanoi**

# Camp Alcatraz




**Rochester & Kiley (1999), Honor Bound: American Prisoners of War in Southeast Asia, 1961-1973**

## ROBERT H. SHUMAKER

**Commander - United States Navy**
**Shot Down: February 11, 1965**
**Released: February 12, 1973**

Cdr. Robert Shumaker was flying an F-8 Crusader when he was hit by 37 mm. cannon fire, which forced the jet out of control. He ejected and his parachute opened a mere 35 feet from the ground. The impact broke his back and he was captured immediately, placed in a jeep and transported over the rutted roads to Hanoi. Upon arrival in Hanoi a white smocked North Vietnamese gave him a cursory examination before dozens of photographers, yet did not give him any medical attention. His back healed itself, but it was six months before he could bend.

The day after he was shot down, he was paraded before a news conference in Dong Hoi by guards with fixed bayonets. A report said that his face showed no signs of remorse. He was asked why the United States was bombing North Vietnam and he answered, "It is in retaliation for the unprovoked aggression of the Communists."

His family was quoted in the press as saying that this was typical of him and that any further statements about him would be Communist propaganda. His former associates also stated that it was like him to stand by what was honest in the middle of enemies.

In the torture sessions he continued to hold out for his beliefs. His back healed, but was reinjured two years later in a torture session because he refused to play the part of a wounded American in a propaganda movie. After beating him they used him for the part anyway.

He was known as one of the "Alcatraz Eleven" because he spent nearly three years in solitary confinement, much of the time clamped in leg irons. He would often think of his young son, Grant, who was just a baby when he was shot down. That little boy was eight years old when he saw him again.

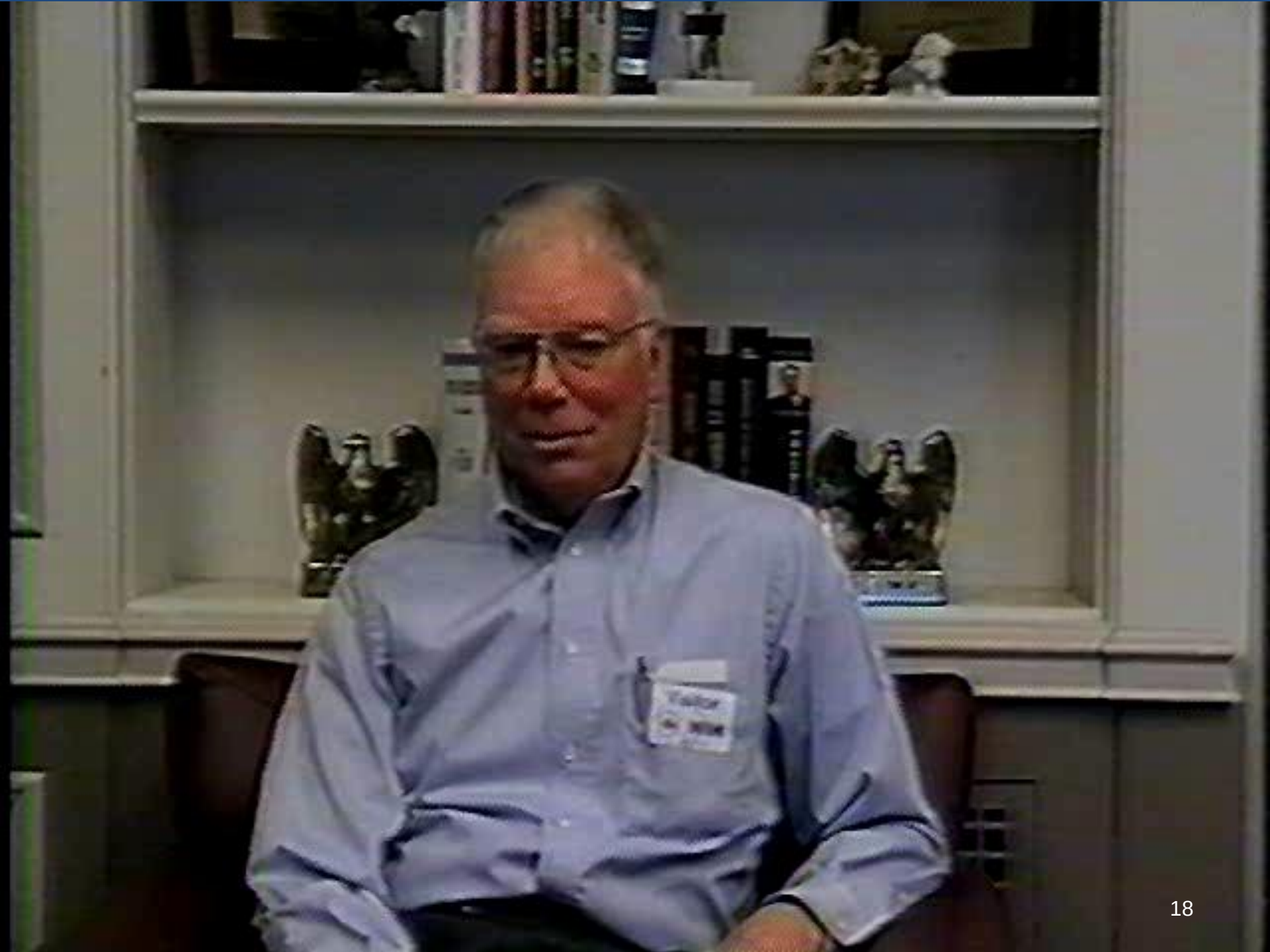
Commander Shumaker originated the name "Hanoi Hilton" for the prison. The famous name was the ultimate in satire since the prisoners were tortured, starved and insulted rather than treated with hospitality.

Through his entire imprisonment of over eight years, Cdr. Shumaker maintained himself as a military man. He states that "When we were released, we marched to the airplanes to show we were still a military organization."

Born in New Castle, Pa., he was graduated from the U.S. Naval Academy in 1956 and later received his MA from the Naval Postgraduate School. He was captured on February 11, 1965, the second to be shot down and the third longest in captivity. He plans to stay with the Navy until retirement.

He leaves this message: "I simply want to say that I am happy to be home and so grateful to a nation that never did forget us. We tried to conduct ourselves so that America would be as proud of us as we are proud of her. I am very proud to have served my country and pleased that we can return with honor and dignity."

**Captain & Mrs. Frederic Wyatt (1977) "We Came Home"**



# THE RESILIENCE PRESCRIPTION

1. **Positive Attitude**
   - Optimism is strongly related to resilience
   - Optimism is, in part, genetic but can be learned (Cognitive Behavioral Therapy)
   - Neurobiological Mechanisms: Reward circuits, converse of learned helplessness

2. **Cognitive Flexibility through Cognitive Reappraisal**
   - Traumatic experiences can be re-evaluated by altering the perceived value and meaningfulness of the event
   - One can receive a benefit from stress and trauma: one can reframe, assimilate, accept and recover. These skills can be learned.
   - Failure is an essential ingredient for growth
   - Neurobiological Mechanisms: Memory Reconsolidation, Cognitive Control of Emotion, Memory Suppression

3. **Embrace a Personal Moral Compass**
   - Develop a set of core beliefs that very few things can shatter
   - For many, faith in conjunction with strong religious and/or spiritual beliefs is associated with resilience
   - Altruism has been strongly related to resilience. Survivor Mission.
   - Neurobiological Mechanisms: Neural Model of Human Morality, Altruism & Human Evolution

# THE STOCKDALE PARADOX

**Retain faith that you will prevail in the end, regardless of the difficulties.**

**AND at the same time**

**Confront the most brutal facts of your current reality, whatever they might be.**

# EARTHQUAKE IMPACT IN A REMOTE SOUTH ASIAN POPULATION: PSYCHOSOCIAL FACTORS AND POSTTRAUMATIC SYMPTOMS

**Although previous studies have documented the psychological impact of earthquakes, less is known about potentially protective characteristics associated with healthier outcomes. In the present study, 2 samples of survivors were recruited from remote villages in Northwestern Pakistan, 7 and 19 months after the devastating October 2005 earthquake. Female gender, lower education, and closer proximity to the epicenter predicted significantly higher posttraumatic symptom levels. After adjusting for demographic characteristics, distance from the epicenter, and death of close relatives, higher dispositional optimism and higher scores on the Connor-Davidson Resilience Scale were significantly associated with lower symptom levels. The authors' findings in a previously unstudied population suggest that certain potentially protective mechanisms, such as optimism, may be universal regardless of culture of origin.**

*Ahmad S., Feder A., Lee EJ., Wang Y., Southwick SM., Schlackman E., Buchholz K., Alonso A., Charney DS., Journal of Traumatic Stress, Vol. 23, No. 3, June 2010, pp. 408-412 (© 2010)*

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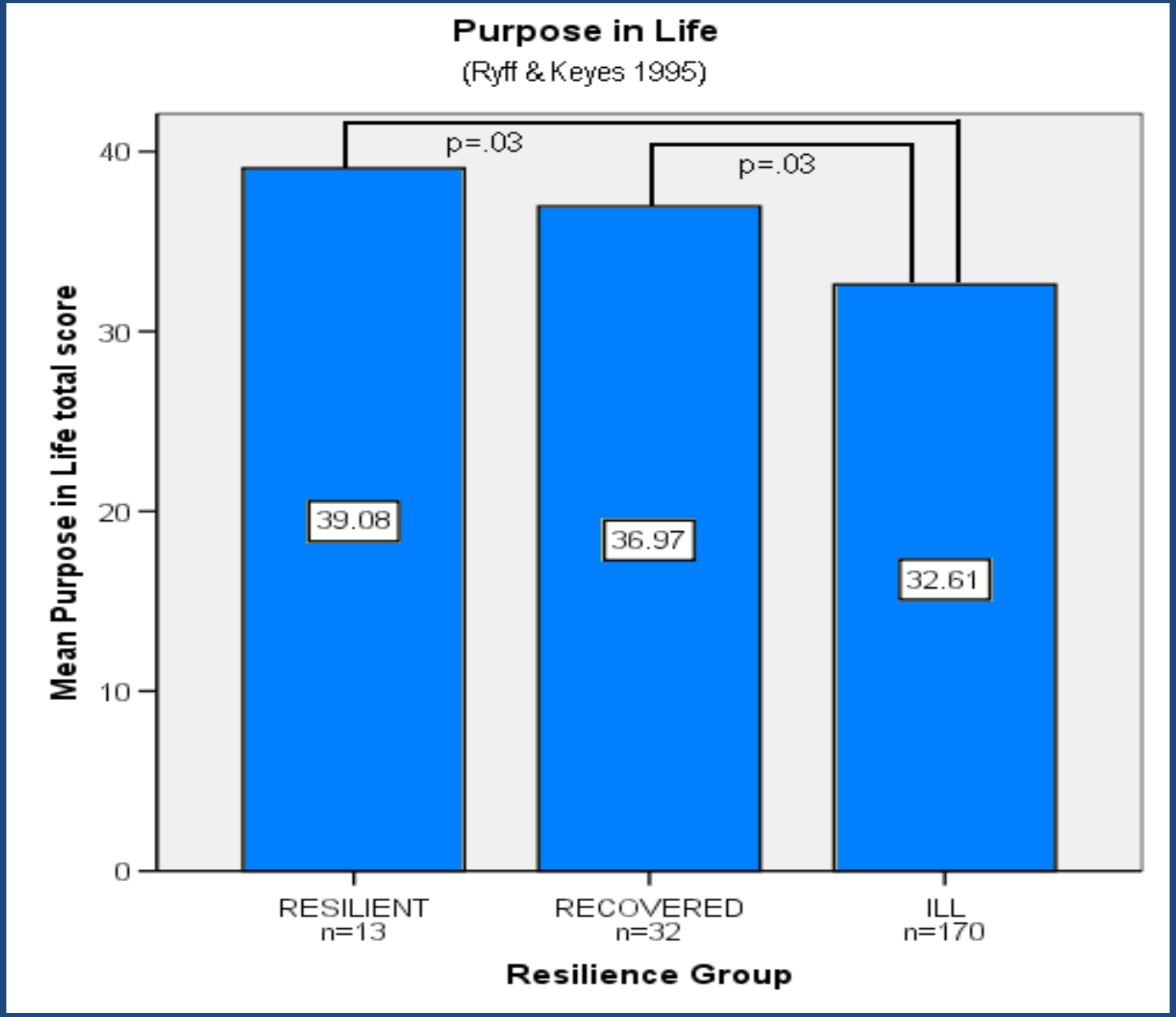
# TRAUMA, RESILIENCE, AND RECOVERY IN A HIGH-RISK AFRICAN-AMERICAN POPULATION

**Method: The sample included 259 patients exposed to at least one severe traumatic event, recruited from primary care offices at Howard University and administered the Structured Clinical Interview for DSM-IV Axis I disorders. Multinomial logistic regression was used to identify potential psychosocial factors associated with resilience and recovery, including purpose in life, mastery, and coping strategies.**

**Results: Forty-seven patients had no lifetime psychiatric disorders (resilient), 85 met criteria for at least one past DSM-IV disorder but no current disorders (recovered), and 127 met criteria for at least one current DSM-IV disorder (currently ill). The resilient group was characterized by a significantly lower lifetime trauma load. Female gender was predictive of currently ill status. In the final model, purpose in life emerged as a key factor associated with both resilience and recovery, and mastery was also significantly associated with recovery.**

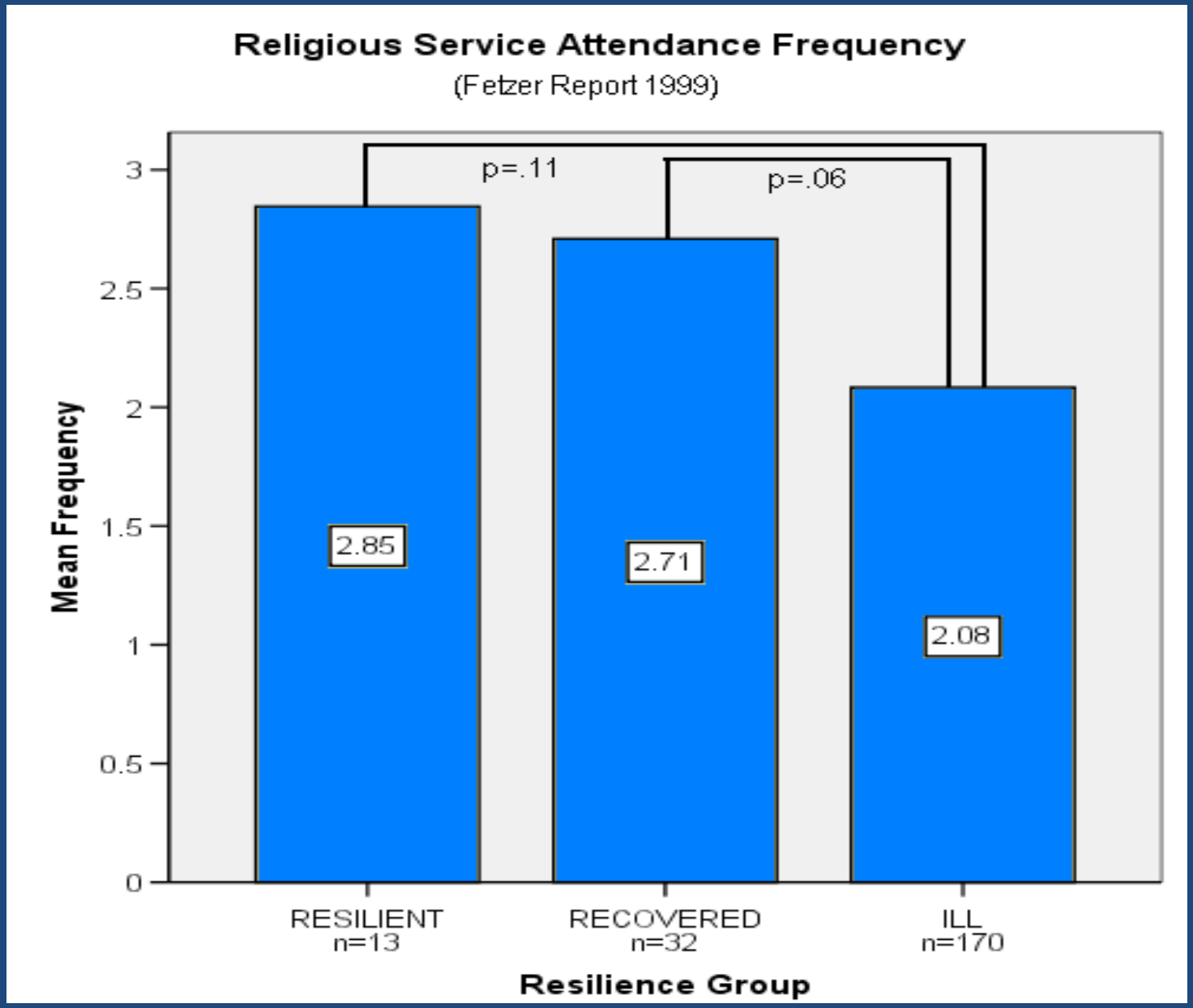
*Alim TN; Feder A; Graves RE; Wang Y; Weaver J; Westphal M; Alonso A; Aigbogun NU; Smith BW; Doucette JT; Mellman TA; Lawson WB; Charney DS.; Am J Psychiatry 2008;165:1566-1575*

# Resilience to Assaultive Trauma




8-item scale, Range 8-56, Higher score = More purpose in life

# Resilience to Assaultive Trauma




**Single-Item, Range 0-5 (0 = Never, 3 = Once or twice a month, 5 = More than once a week)**

# Coping and PTSD Symptoms in Pakistani Earthquake Survivors: Purpose in Life, Religious Coping and Social Support

**Background**: High rates of posttraumatic stress disorder (PTSD) and depressive symptoms have been observed in earthquake survivors from less developed areas of the world. This study, conducted three years after the 2005 Pakistan earthquake, aimed to identify potentially protective psychosocial factors associated with lower PTSD and depressive symptom levels.

**Methods**: Adult earthquake survivors (*N*=200) were recruited from affected areas in Northwestern Pakistan and completed self-report questionnaires measuring PTSD and depressive symptoms, positive and negative affect, and four psychosocial variables (purpose in life, positive and negative religious coping, and social support).

**Results**: Sixty five percent of participants met criteria for probable PTSD. Purpose in life was associated with lower symptom levels and higher positive emotions. A form of negative religious coping (feeling punished by God for one's sins or lack of spirituality) was associated with higher symptom levels and negative emotions. Higher perceived social support was associated with higher positive emotions. Other significant relationships were also identified.

**Limitations**: Limitations include the recruitment of a sample of convenience, a modest sample size, and the cross-sectional nature of the study.

**Conclusions**: Findings suggest that some psychosocial factors may be protective across cultures, and that the use of negative religious coping is associated with poorer mental health outcomes in earthquake survivors. This study can inform preventive and treatment interventions for earthquake survivors in Pakistan and other less industrialized countries as they develop mental health care services.

*Feder A., Ahmad S., Lee EJ., Morgan JE., Singh R., Smith BW., Southwick SM, Charney DS., Journal of Affective Disorders (2012), http://dx.doi.org/10.1016/j.jad.2012.10.027*

# THE RESILIENCE PRESCRIPTION

## 4. Find a Resilient Role Model

- Role models can be found in one's own life
- Imitation is a very powerful mode of learning
- Neurobiological Mechanisms: Neuronal Imprinting of Human Values

## 5. Face Your Fears

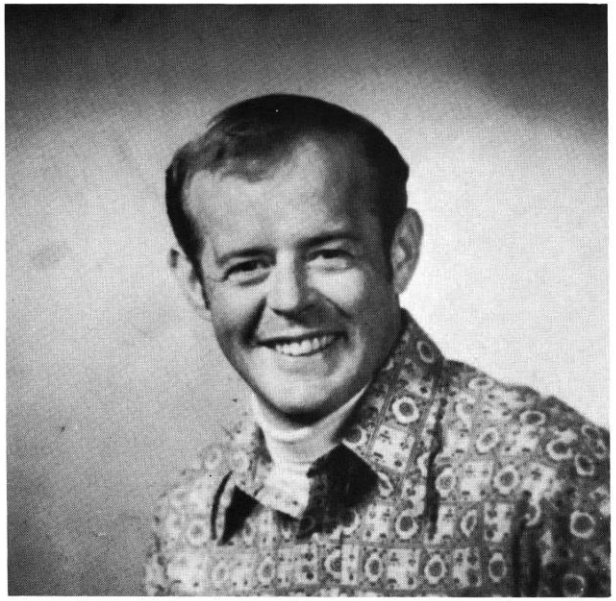
- Fear is normal and can be used as a guide
- Facing your fears can increase your self-esteem
- Learn and practice skills necessary to move through the fear
- Neurobiological Mechanisms: Extinction, Stress Inoculation

## 6. Develop Active Coping Skills

- Resilient individuals use active rather than passive coping skills
- Minimize appraisal of threat, create positive statements about oneself, seek support of others, & ACT
- Neurobiological Mechanisms: Functional Neuroanatomy of Fear Mechanisms

## STEPHEN G. LONG

**Captain - United States Air Force**
**Shot Down: February 28, 1969**
**Released: March 28, 1973**



My first assignment after completing pilot training at Williams AFB in Arizona was the O-2 FAC aircraft flying out of Thailand. After 3 months of flying in Laos I went on 4 years of inactive type service in Hanoi.

After being confined for this period of time, the urge to fly has grown even stronger. Although I wanted to return to flying as soon as possible, I felt that attending Squadron Officers' School (SOS) would help me make the adjustment back into active duty military life.

I graduated from SOS on 30 November 1973 and after a wonderful first Christmas home with my family, I got my first flight in the T-38 recurrency program on 11 January 1974. Upon completion of that program I will be stationed at Homestead AFB, Fla., flying the F-4E.

It has taken some time to understand what has happened since my release. There is no way I could ever have known how much energy and effort was being exerted for the interests of the POW's, nor the limits of the genuine sympathy, attention, and love given to ourselves. I was quite overwhelmed and I feel that I owe a great deal to all those who helped to obtain our release by bringing attention to our plight, and making our release a most wonderful and memorable experience.

I will never be able to express my deep appreciation to all these wonderful people and relate to them my gratitude—but I will try. To all of you—Thank you!



**Captain & Mrs. Frederic Wyatt (1977) "We Came Home"**

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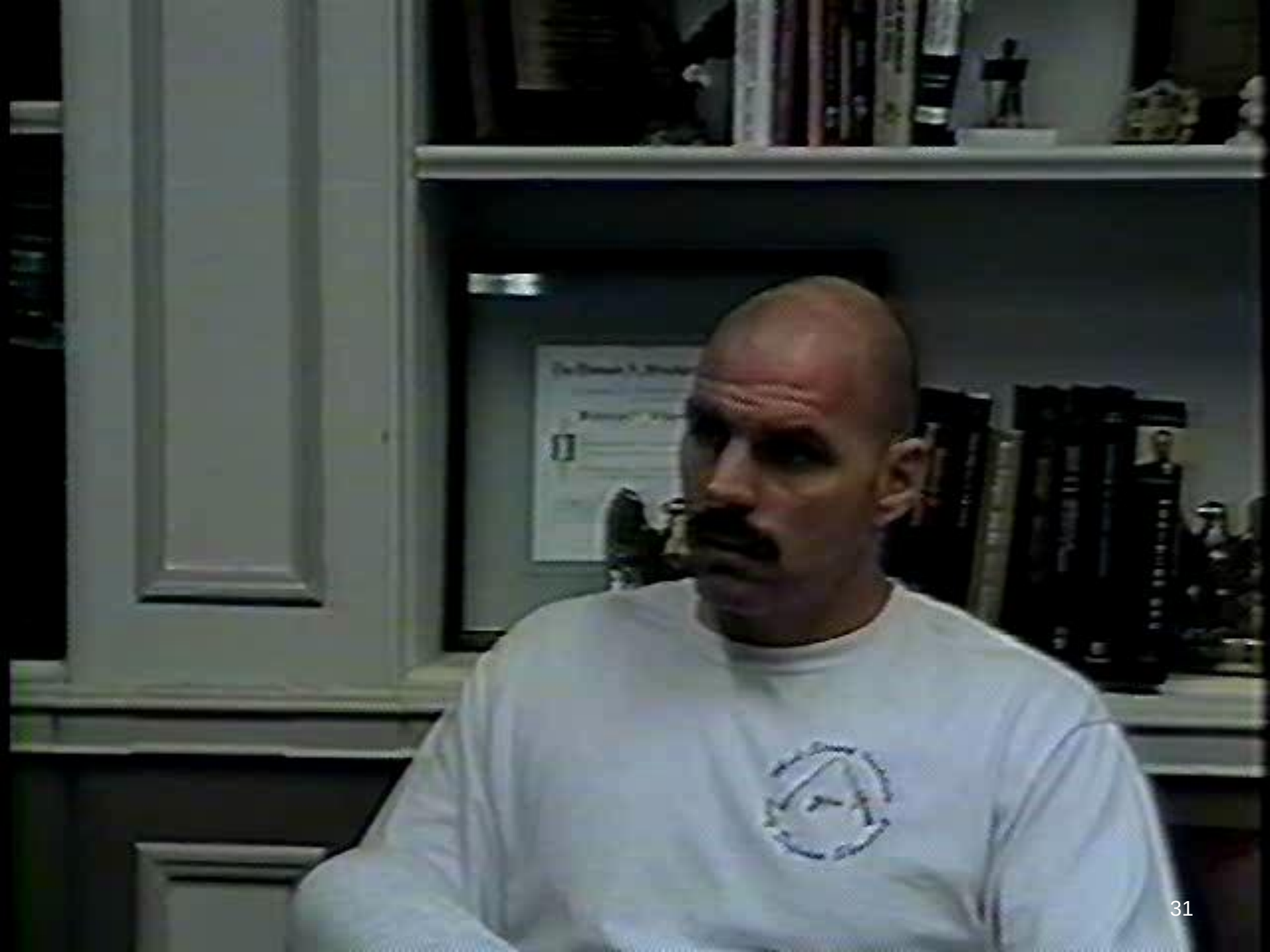


# THE RESILIENCE PRESCRIPTION

## 7. Establish and Nurture a Supportive Social Network

- Very few can "go it alone"
- Considerable emotional strength accrues from close relationships with people and organizations
- A safety net during times of stress
- Neurobiological Mechanisms: Cognitive Neuroscience of Human Social Behavior

## 8. Attend to Physical Well-being

- PE has positive effects on physical hardiness, mood, and improves self-esteem
- Neurobiological Mechanisms: Effects on neurogenesis, cognition, regulation of emotion, immune function, etc.

# THE ROLE OF COPING, RESILIENCE, AND SOCIAL SUPPORT IN MEDIATING THE RELATION BETWEEN PTSD AND SOCIAL FUNCTIONING IN VETERANS RETURNING FROM IRAQ AND AFGHANISTAN

**Posttraumatic stress disorder (PTSD) is one of the most common psychiatric disorders among veterans returning from Iraq and Afghanistan. Little research has examined variables that may mediate the relation between PTSD and aspects of social functioning, such as relationship satisfaction and family functioning. In this cross-sectional study, a total of 164 veterans who were seeking VA primary care or mental health care within one year after returning from Iraq and/or Afghanistan were screened for PTSD and completed a series of questionnaires that assessed social functioning, coping, and life satisfaction. Results showed that the 86 (52%) veterans who screened positive for PTSD reported greater difficulties in their relationships with romantic partners, less cohesion in their families, less social support, poorer social functioning, and lower life satisfaction compared to other treatment-seeking veterans. Less social support from the community, excessive worry, decreased acceptance of change, and lower availability of secure relationships mediated the association between PTSD and poor social functioning. The relation between PTSD and lower partner satisfaction was mediated by greater cognitive social avoidance and lower availability of secure relationships. These results suggest that psychotherapeutic interventions that address these mediating variables may help improve social functioning in treatment-seeking veterans with PTSD.**



*Tsai J, Harpaz-Rotem I, Pietrzak RH, Southwick SM., Psychiatry, 2012 Summer; 75(2):135-49*

# PSYCHOLOGICAL RESILIENCE IN OEF-OIF VETERANS: APPLICATION OF A NOVEL CLASSIFICATION APPROACH AND EXAMINATION OF DEMOGRAPHIC AND PSYCHOSOCIAL CORRELATES

**A growing number of studies have examined the prevalence and correlates of psychopathology in Veterans of Operations Enduring Freedom and Iraqi Freedom (OEF-OIF), but few have examined determinants of resilience in this population. This study employed a novel approach to classify psychological resilience in a cross-sectional sample of OEF-OIF Veterans. A total of 272 predominantly older reserve/National Guard OEF/OIF Veterans completed a mail survey that assessed combat exposure, psychopathology, psychosocial functioning, and aspects of social support. Cluster analysis of scores on measures of combat exposure and PTSD symptoms revealed that a three-group solution best fit the data: Controls (low combat exposure, low PTSD symptoms); PTSD (high combat exposure, high PTSD symptoms); and Resilient (high combat exposure, low PTSD symptoms). Compared to the PTSD group, the Resilient group was more likely to be in a relationship and active duty; they also scored lower on a measure of psychosocial dysfunction, and higher on measures of psychological resilience and postdeployment social support. Logistic regression analysis revealed that being in a relationship, having fewer psychosocial difficulties, and reporting greater perceptions of purpose/control and family support and understanding were significantly associated with resilient group membership. Results of this study demonstrate a novel approach to classifying psychological resilience and suggest that interventions to mitigate psychosocial difficulties, enhance perceptions of purpose and control, and bolster family support and understanding may help promote resilience to combat-related PTSD in OEF-OIF Veterans.**



*Pietrzak RH, Southwick SM., J Affecti Disord 2011 Oct; 133(3):560-8. Epub 2011 May 31*

**LEWIS E. MEYER**
Civilian
Captured: February 1, 1968
Released: March 27, 1973


I was born in San Diego, California on 3 August 1933. I served in Korea while with the US Army from 8 May 1951 to 7 May 1954. After my discharge from the Army I joined the Federal Fire Department where I served as crash fire supervisor at NAS North Island, Miramar and at Cubi Point in the Philippine Islands. In October of 1967 I was assigned to the NAS Da Nang as Assistant Fire Chief in charge of co-ordinating and standardizing fire departments in I Corp. While on an inspection trip in the northern part of I Corp I was captured with ground forces in Hue during the 1968 Tet offensive. I was held by the North Vietnamese Army for 62 months and was released in Hanoi on March 27, 1973.

My wife's name is Gail and we have two sons, Bill, age 20, a student at the University of California at San Diego, and Jeff, age 17, a senior at Kearney High School.

**Captain & Mrs. Frederic Wyatt (1977) "We Came Home"**

# THE RESILIENCE PRESCRIPTION

**General Principles (we underestimate capacities of Mind, Brain, Body)**

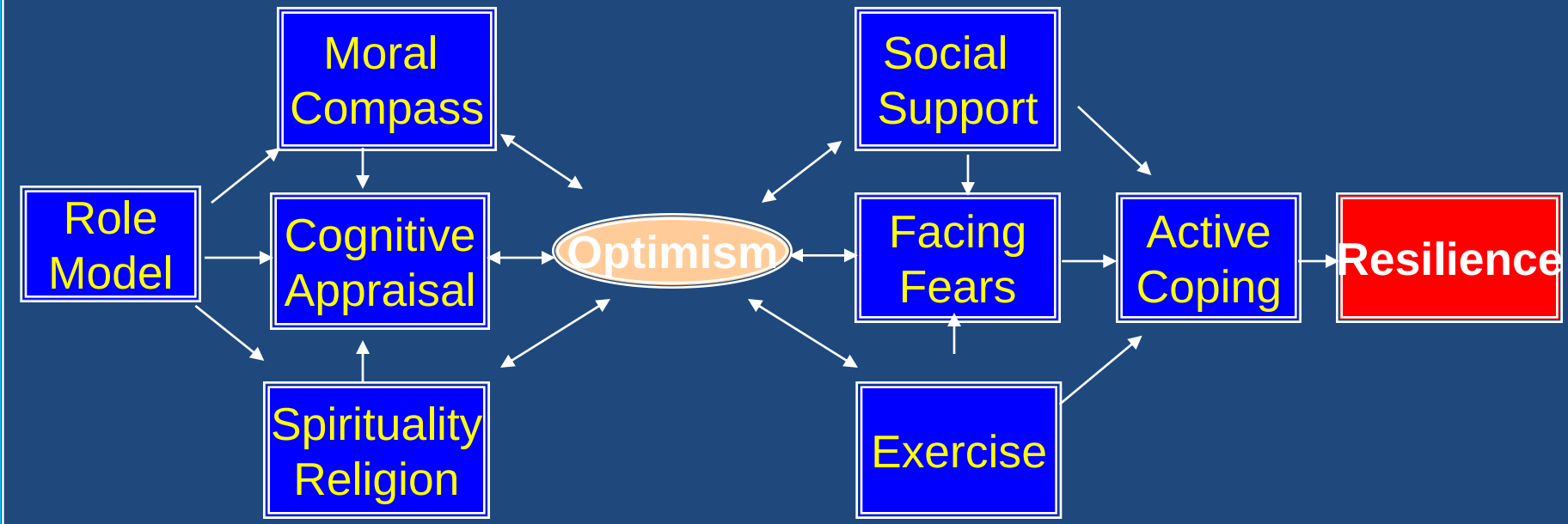
**9. Train Regularly and Rigorously in Multiple Areas**

- Change requires systematic and disciplined activity
- Concentrate on training in multiple areas: emotional intelligence, moral integrity, physical endurance

**10. Recognize, Utilize & Foster Signature Strengths**

- Learn to recognize your character strengths and engage them to deal with difficult & stressful situations.

Signature Strengths



ENVIRONMENTAL STRESSORS
AND
GENETIC PREDISPOSITION

| | Depression Risk Factors | Therapeutic Intervention | Resilience Protective Factors |
|---|---|---|---|
| COGNITIVE/BEHAVIORAL | Weak executive function; weak coping self-efficacy; negative attention bias; cognitive inflexibility | CBT with cognitive reappraisal; positive emotion exercises, coping skill development and training; well-being therapy | Strong executive function; high coping self efficacy; positive emotions; realistic optimism; cognitive flexibility |
| EMOTION REGULATION | Weak regulation (e.g. anhedonia; slow stress recovery) | Mindfulness; training; antidepressant medications | Strong regulation (e.g. delay gratification; rapid stress recovery) |
| SOCIAL | Weak social skills; minimal social network; no resilient role models | Social emotional training; network support treatment | Strong social skills; diverse social network; resilient role models |
| PHYSICAL HEALTH | Sleep deprivation; poor cardiovascular fitness; poor nutrition; obesity | Teach sleep hygiene; exercise regimen; improve diet | Strong sleep habits; physically fit; good nutrition |
| NEUROBIOLOGY | Dysregulated HPA axis and SNS in response to stress; attenuated prefrontal cortical executive function and stress induced limbic system hyperactivity | Neural circuit training; novel medications (NPY, CRF, GABA, glutamate) | Effective regulation of HPA axis and SNS in response to stress; robust prefrontal cortical executive function and capacity to regulate limbic reactivity to stress |

Southwick SM, Charney DS; Science Vol 338, October 2012

# DEVELOPMENT OF RESILIENCE

## EARLY LIFE STRESS AND VULNERABILITY

**Early physical and sexual abuse is associated with long-lasting interrelated hormonal, neurotransmitter and CNS changes that are likely to mediate increased vulnerability to psychiatric disorders into adulthood.**

# DEVELOPMENT OF RESILIENCE

## RESILIENCE TO EARLY LIFE STRESS

**Studies in children adopted away from institutional orphanages in Romania illustrate the capacity of adaptive systems to resist or recover from marked disturbances when they are healthy and functional.**

- **Caring Adult**
- **Social Competence**
- **Capacity for Self Reflection and Self Regulation**

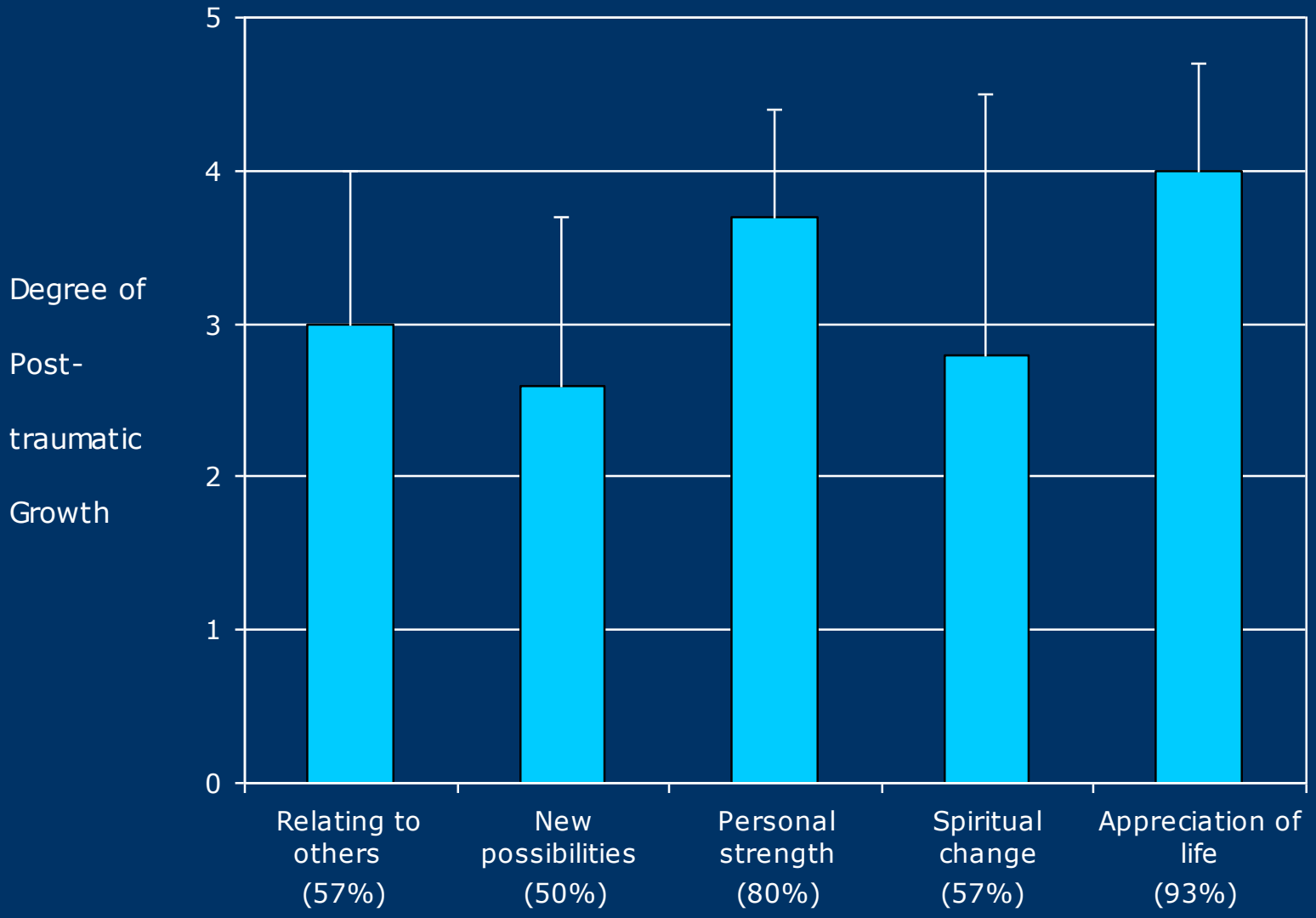
# DEVELOPMENT OF RESILIENCE

## STRESS INOCULATION

It is also likely that exposure to manageable stressors during development is associated with more adaptive coping with stress during adulthood. In studies of squirrel monkeys and rodents, early exposure to manageable stressors ('stress inoculation') was found to be associated with reduced behavioural and hormonal responses to stress later in life. Adaptive responses seem to be associated with the degree of behavioural control an animal has over stress.

# Posttraumatic Growth in Vietnam POWs

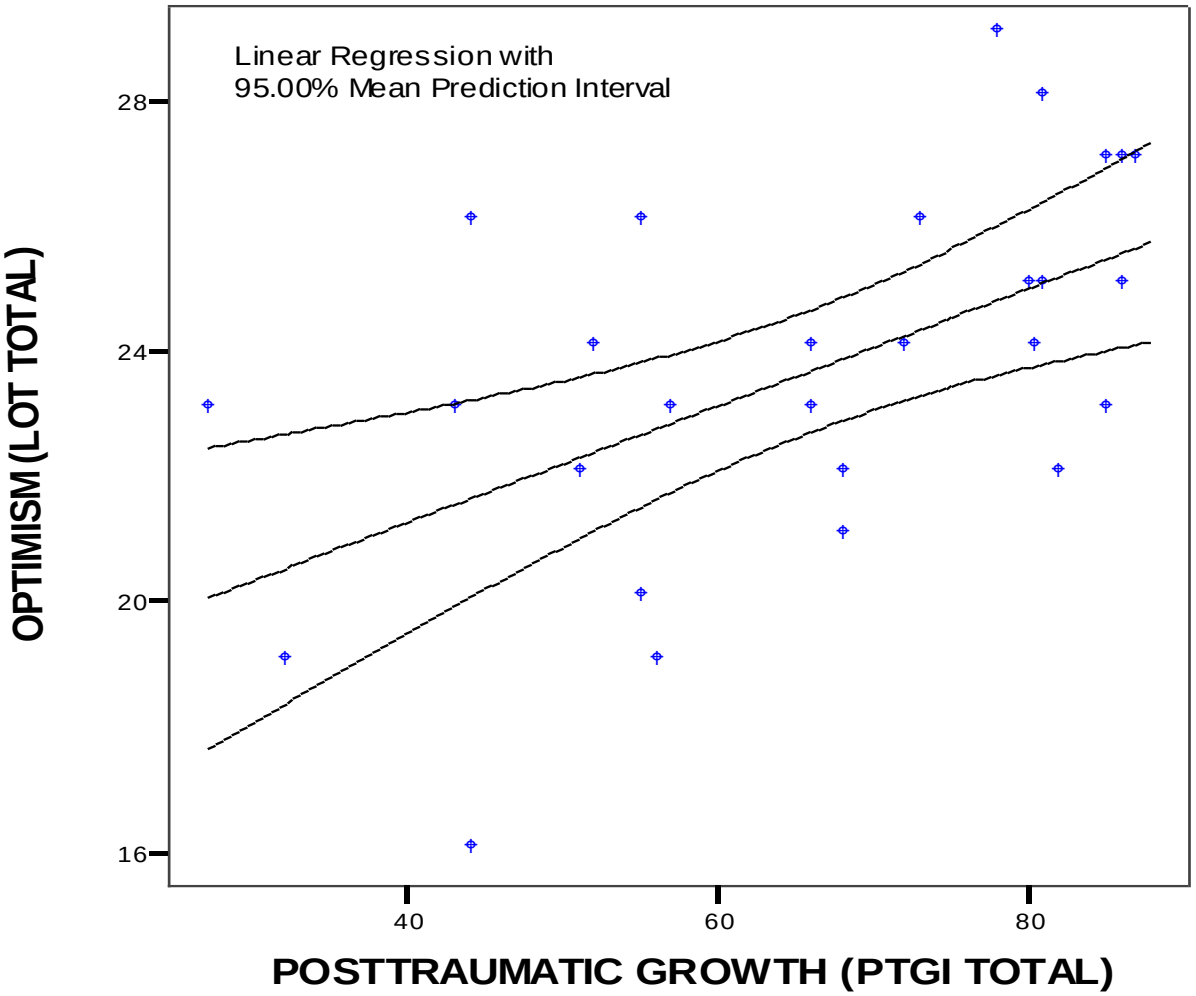
(PTGI)




% with mean score ≥ 3

PTGI = Posttraumatic Growth Inventory; mean score range = 0-5
n = 30

# POSTTRAUMATIC GROWTH AND OPTIMISM IN VIETNAM POWS




**PTGI = Posttraumatic Growth Inventory (total score = 0-105)**

**LOT = Life Orientation Test (total score = 6-30)**

**n = 28**
**r = .55**
**p = .002**

**“In the total sense of my life, it's probably been a good experience for me… I wouldn't erase the experience, because I got benefits out of it. I can't erase it. I can't go back and change it…Frankly, it left permanently more good things in my life than it did bad things…Pain creates character…I'm not volunteering to go back, but it's happened. I'll take advantage of the good things…If you can endure pain, you'll learn how to get through hard things. You just become tougher emotionally.”**

***Tom Collins***

# DEVELOPMENT OF RESILIENCE

## GENETIC INFLUENCES ON RESILIENCE

1. **HPA AXIS – Related Genes**
   - **CRH Type 1 Receptor Gene**
   - **Glucocorticoid Receptor Genes**
2. **Neuropeptide Y**
3. **Brain Derived Neurotrophic Factor (BDNF)**
4. **Serotonin Transporter**

# ALLOSTATIC LOAD AND SUCCESSFUL AGING

**12-hr overnight urinary excretion of cortisol**
**12-hr overnight urinary excretion of norepinephrine**
**12-hr overnight urinary excretion of epinephrine**
**Serum DHEA-S**
**Average systolic blood pressure**
**Average diastolic blood pressure**
**Ratio of waist-hip circumference**
**Serum high density lipid (HDL) cholesterol**
**Ratio of total to HDL cholesterol**
**Blood glycosolated hemoglobin**

**Allostatic load summary measure is significantly associated with:**

- **new cardiovascular events**
- **decline in cognitive functioning**
- **decline in physical functioning**
- **mortality**

*Seeman et al (2001), PNAS, 98, 4470*

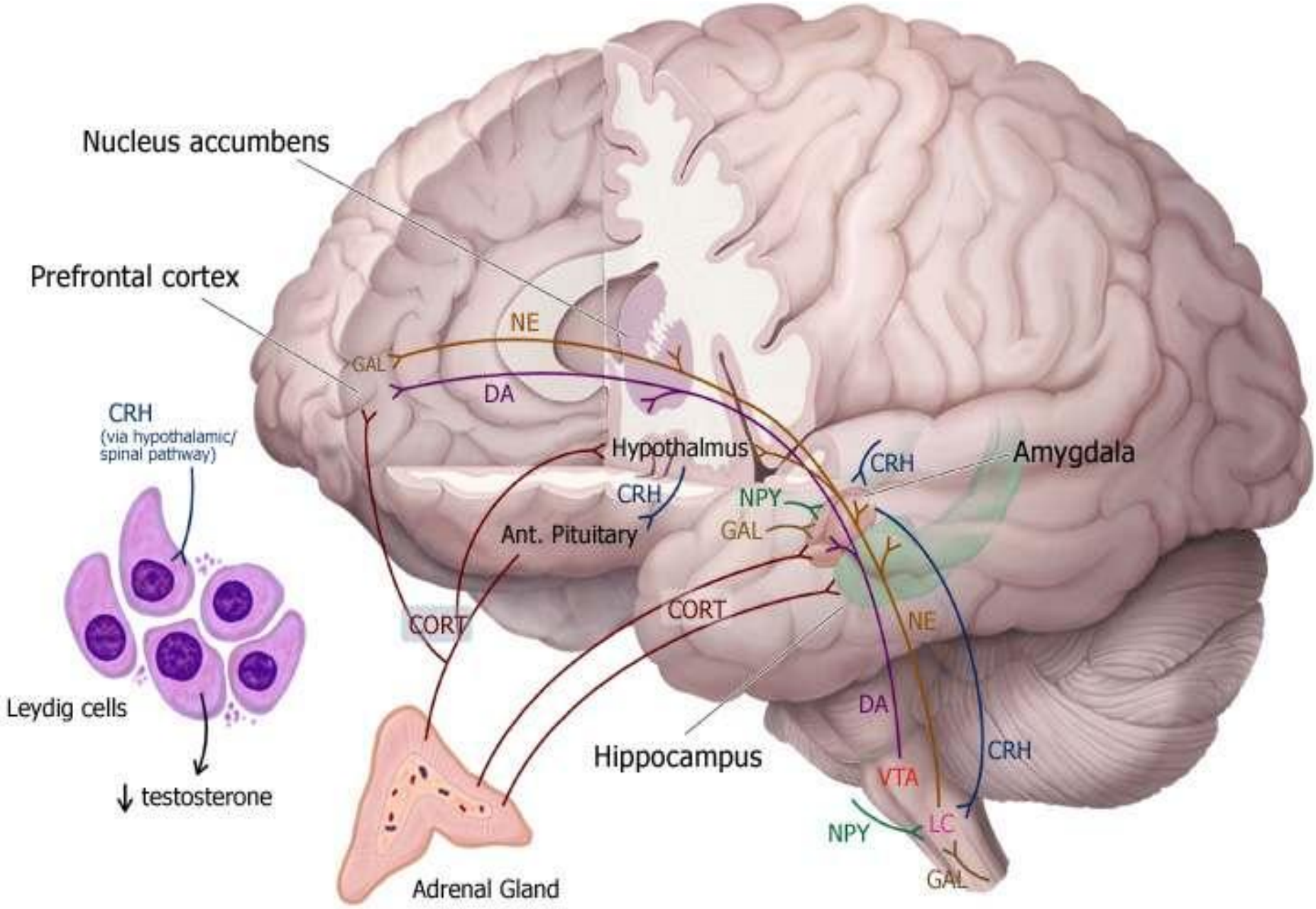
# NEUROCHEMICAL SYSTEMS RESPONDING TO ACUTE STRESS

Cortisol
Dehydroepiandrosterone (DHEA)
Corticotropin Releasing Hormone (CRH)
Locus Coeruleus Norepinephrine
Neuropeptide Y (NPY)
Galanin
Dopamine (DA)
Serotonin (5HT)
Benzodiazepine Receptors
Testosterone
Estrogen

**McEwen and Stellar hypothesized that the cumulative impact on health risk from modest dysregulations in multiple systems can be substantial, even if they individually have minimal and insignificant health effects. Thus, they defined allostatic load as a cumulative measure of physiological dysregulation over multiple systems.**



*McEwen BS & Stellar E (1993), Arch Intern Med, 153, 2093*


Nucleus accumbens
Prefrontal cortex
NE
GAL
DA
CRH
(via hypothalamic/
spinal pathway)
Hypothalmus
CRH
Ant. Pituitary
NPY
GAL
CRH
Amygdala
CORT
CORT
NE
DA
CRH
VTA
NPY
LC
GAL
Hippocampus
Leydig cells
↓ testosterone
Adrenal Gland

# Survival

# .....Evasion

# .....Resistance

# .....Escape

**SERE training is brutal. Special Forces candidates undergo weeks of grueling emotional and physical stress that includes sleep deprivation and excruciating physical demands. Trainees must endure cold, dark, hunger, abusive interrogation, grueling exercise, while performing heart-racing cognitive challenge drills during these extreme situations. Performing well in their vulnerable (exhausted, hungry, cold, etc.) state helps prepare them for the unknowns of special operations. "Stress Inoculation" and operant conditioning are key principles of SERE training. Precision thinking and instant vigorous response, under unimaginable circumstances, is the goal.**

**"It is imprinted in my brain"**

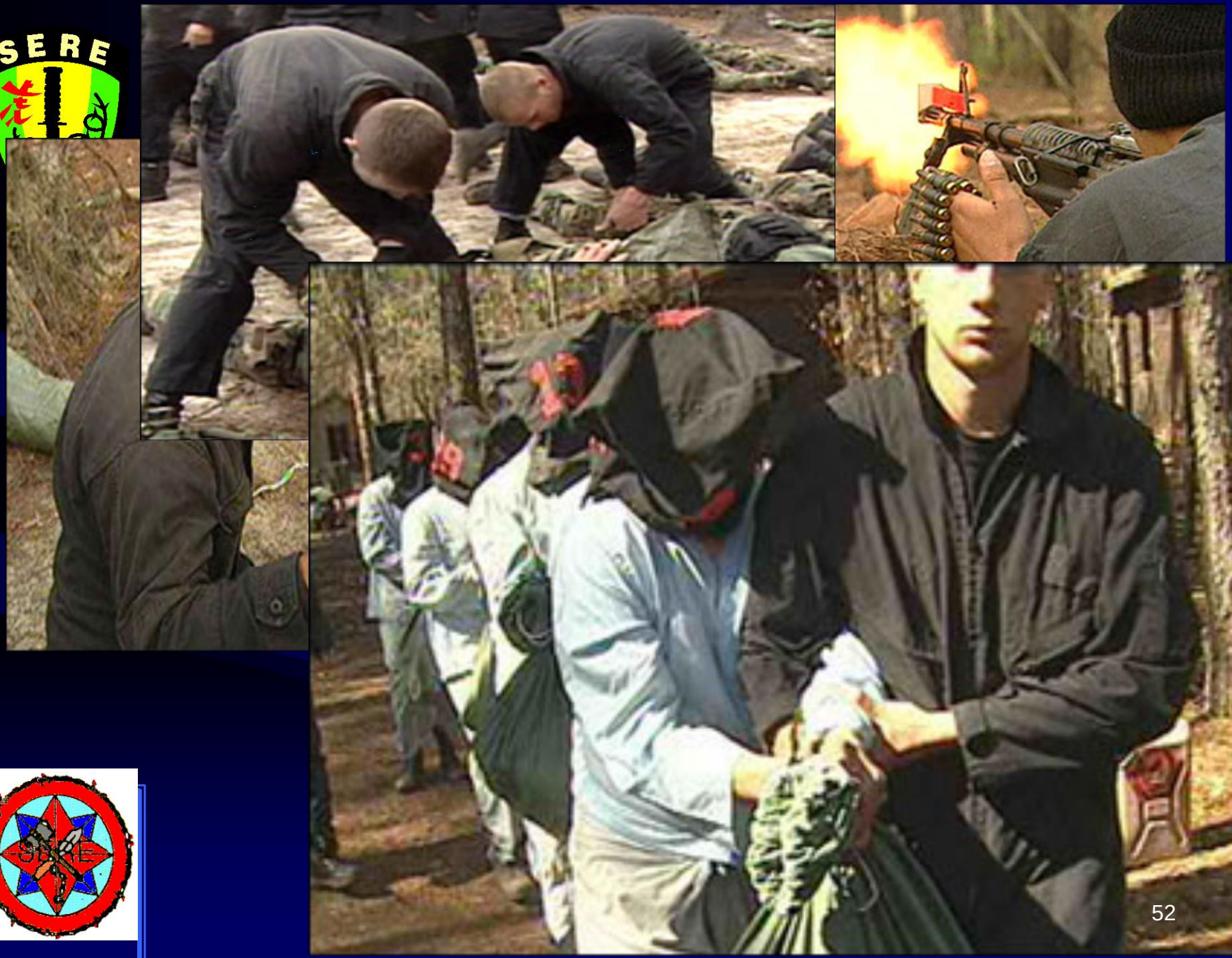
**Maj. Chris Miller, U.S. Special Forces, when asked about SERE**

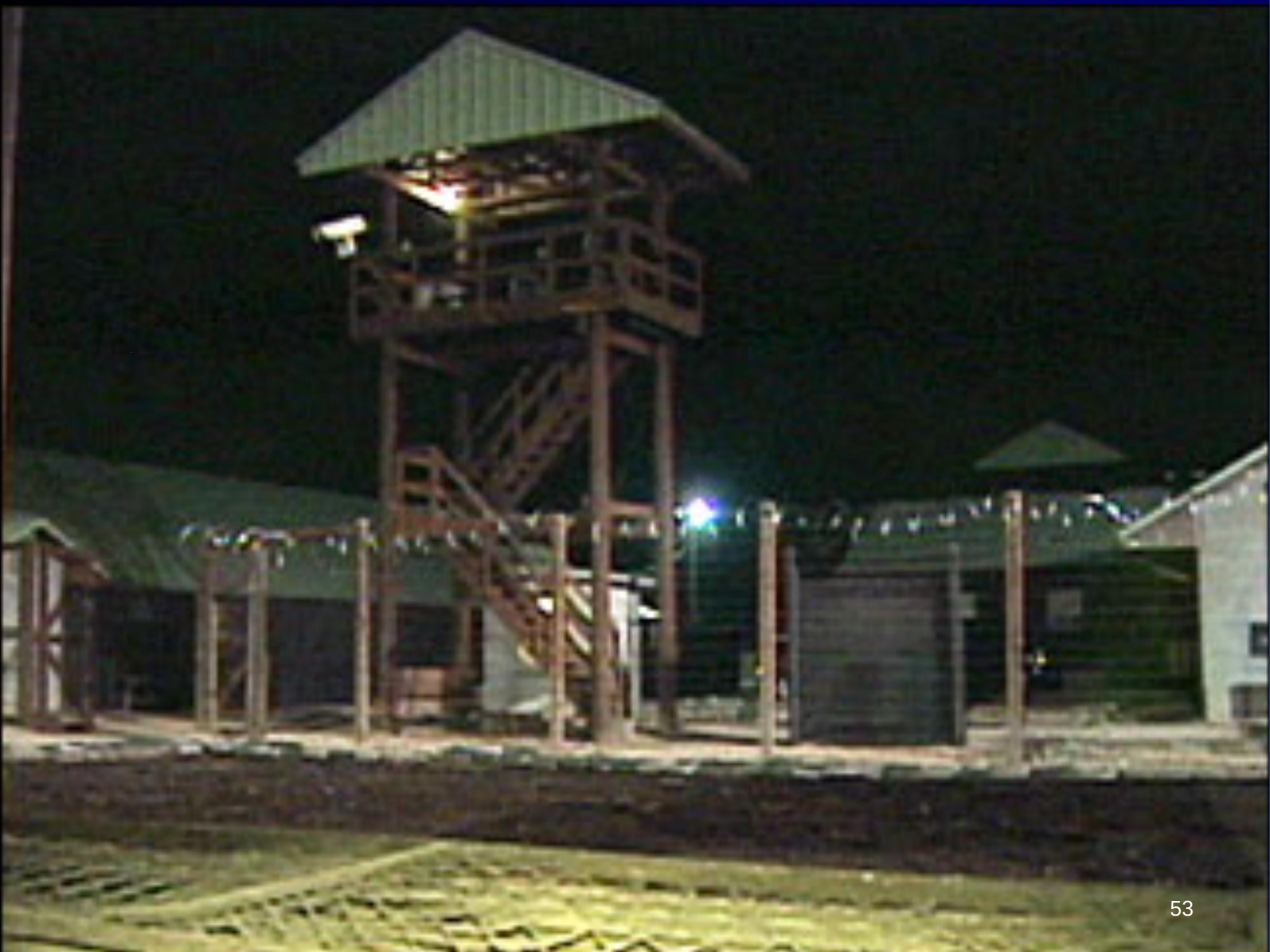


*Mass, P., The New York Times Magazine, Nov. 10, 2002, pp 52-57*

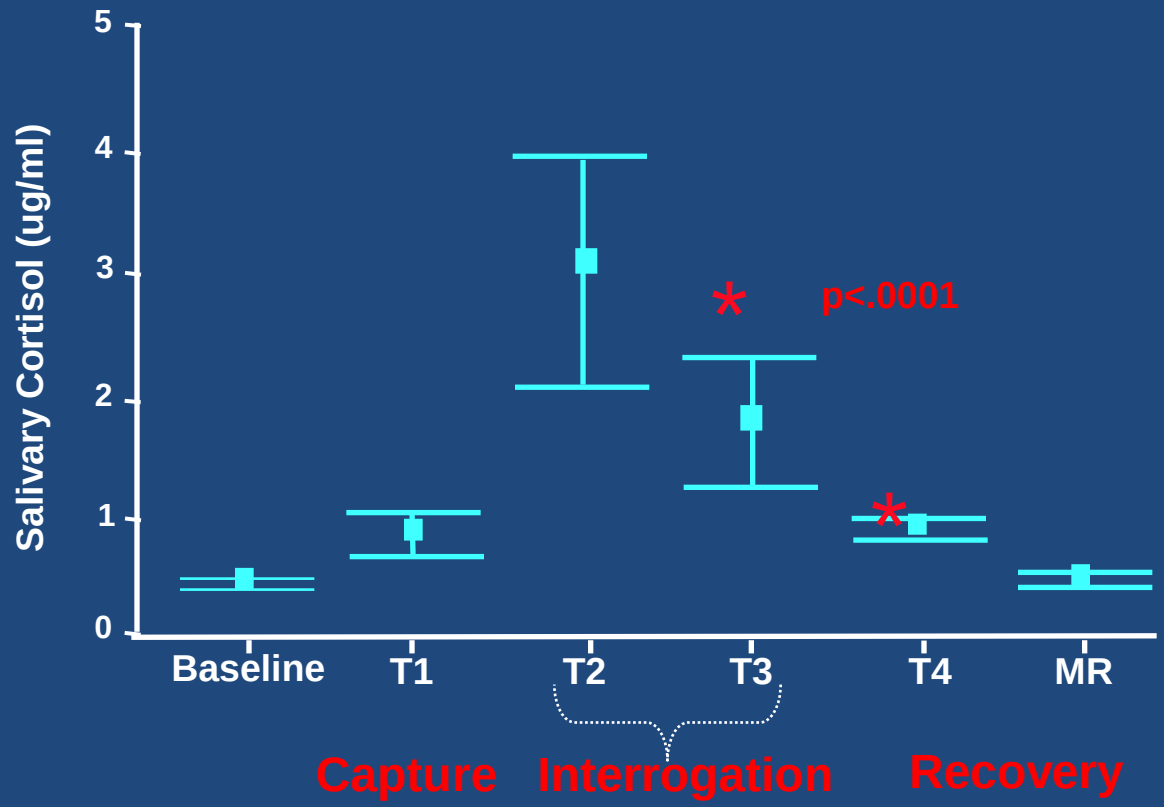
# SURVIVAL SCHOOL IS DIVIDED INTO FOUR PHASES:

- A pre stress, didactic phase (classroom instruction)
- An Evasion phase where subjects are hunted in the wilderness.
- A confinement phase in a mock POW camp
- A debriefing, post stress phase that ends with graduation from the course.


SERE

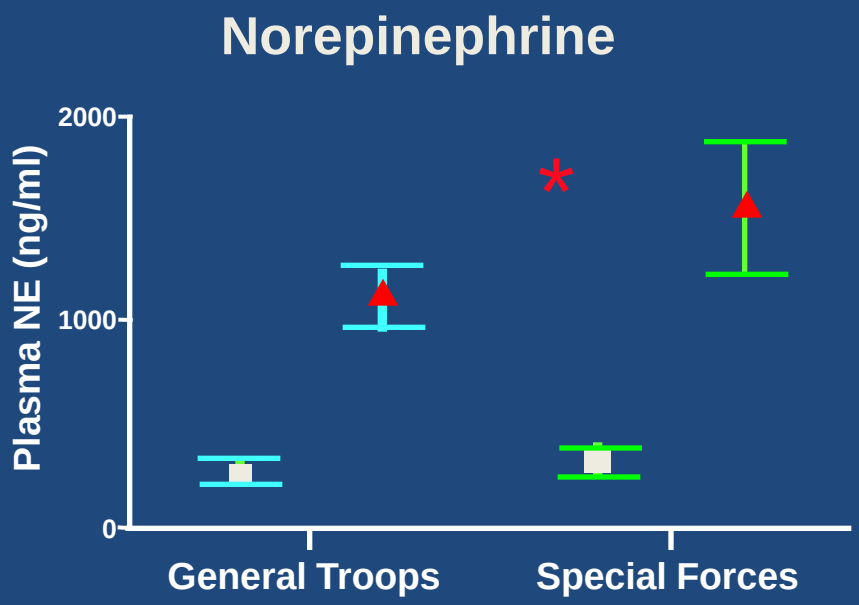


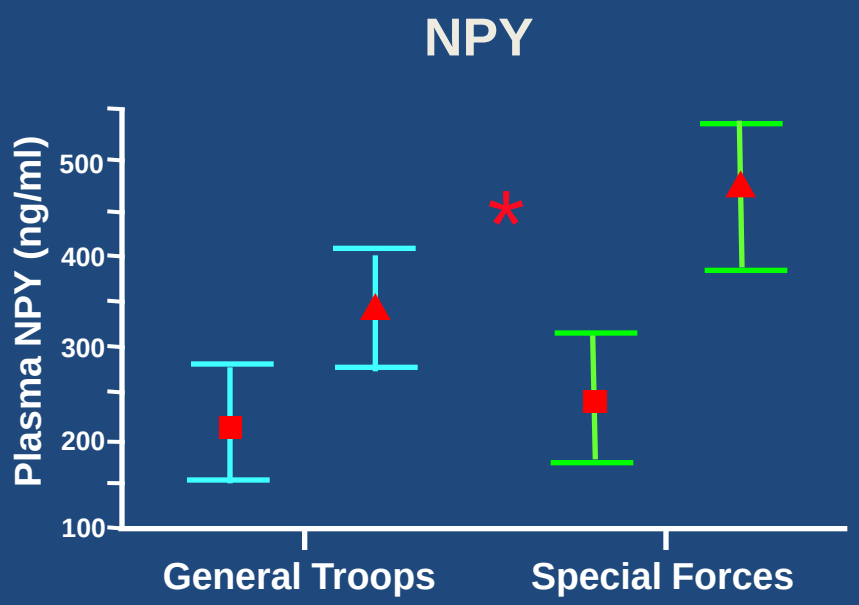
# ELEVATED CORTISOL LEVELS DURING US ARMY TRAINING COURSE

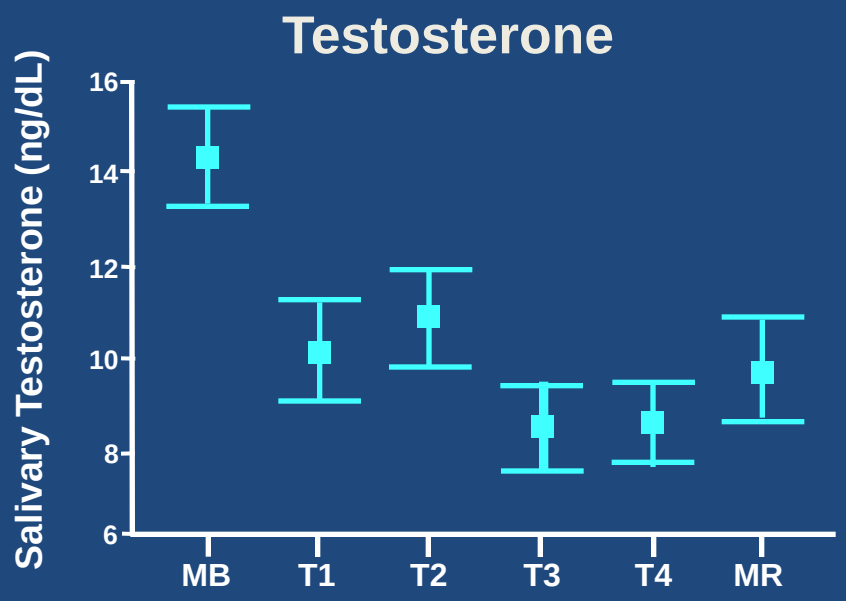


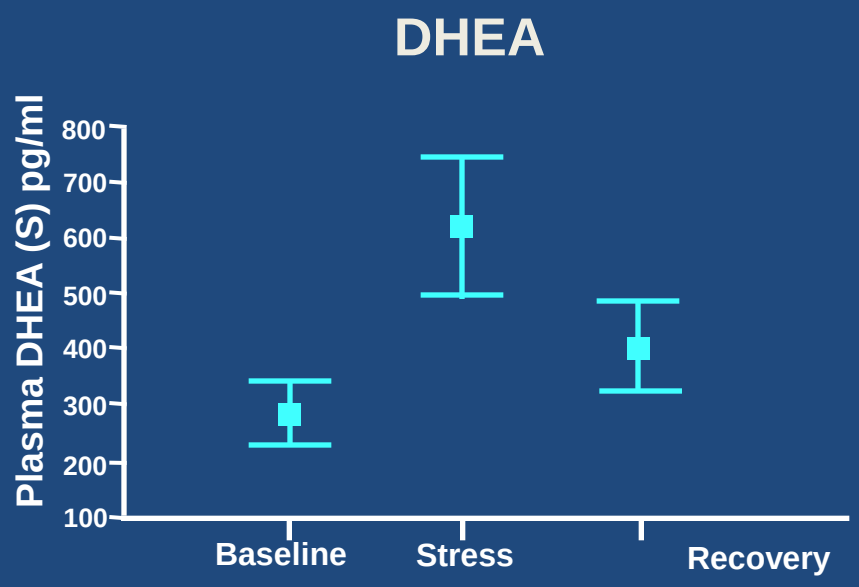

*Morgan 2000*

# HORMONAL CHANGES IN ACUTE STRESS



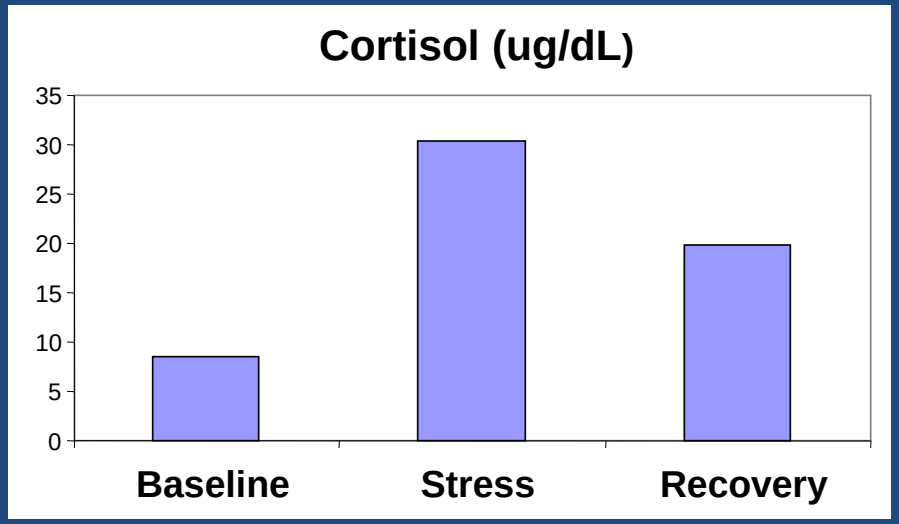



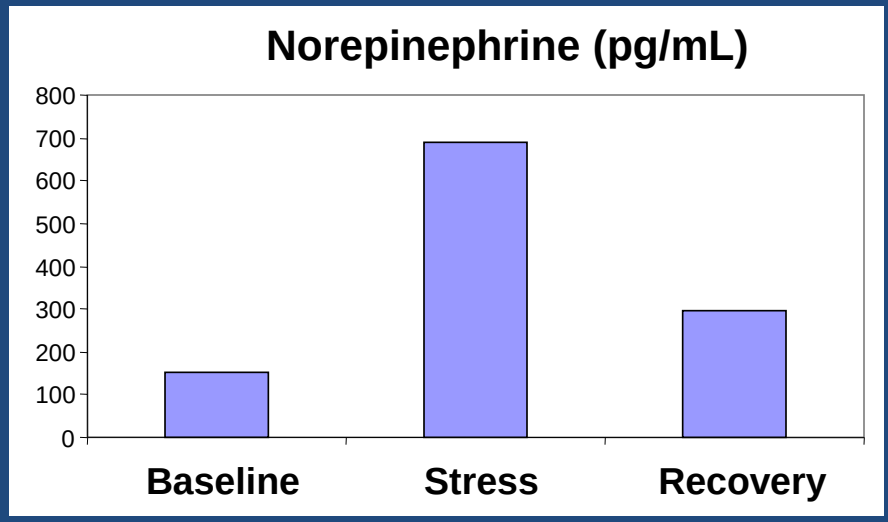



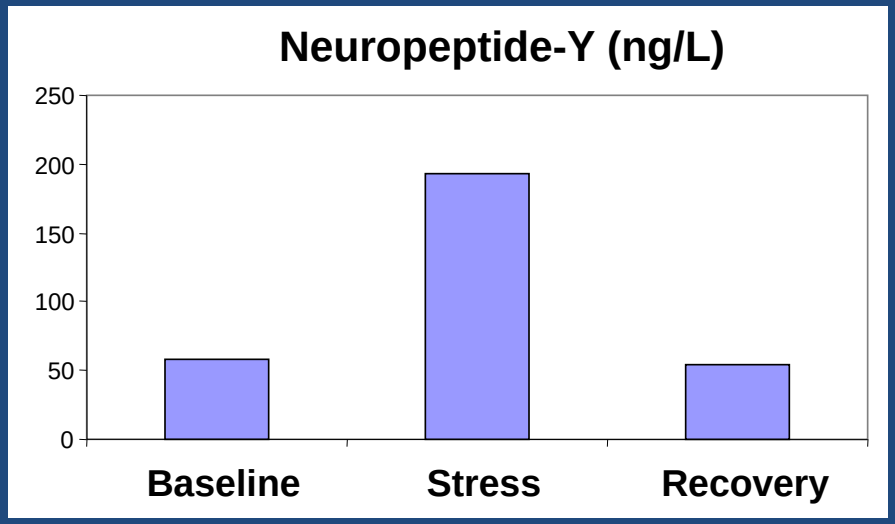




*Morgan 2000 and Morgan 2001*

# NEUROCHEMICAL RESPONSES TO STRESS
# NAVY SEAL SURVIVAL SCHOOL

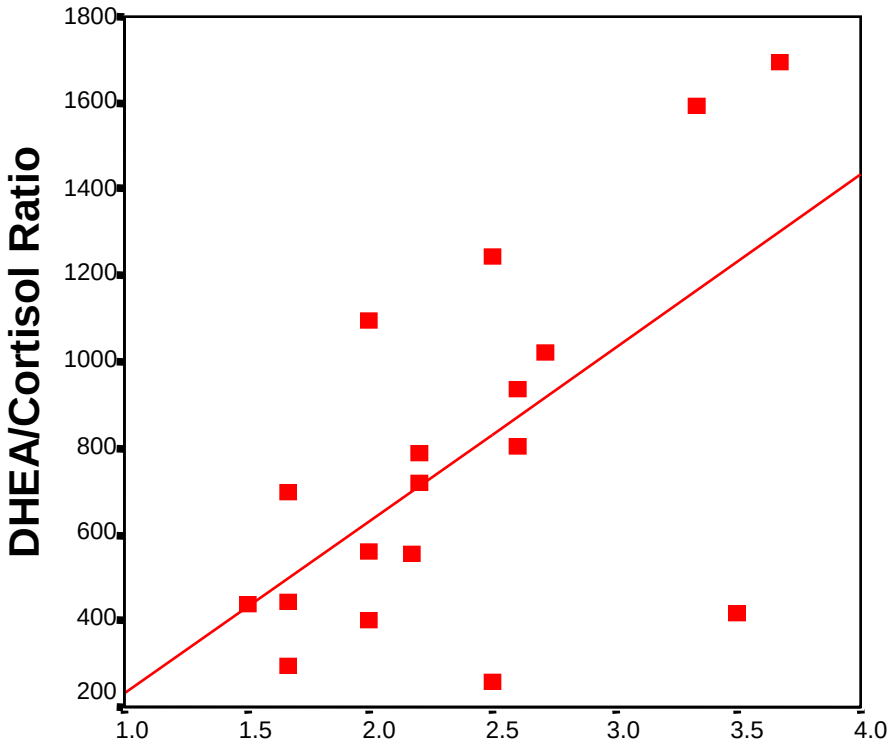


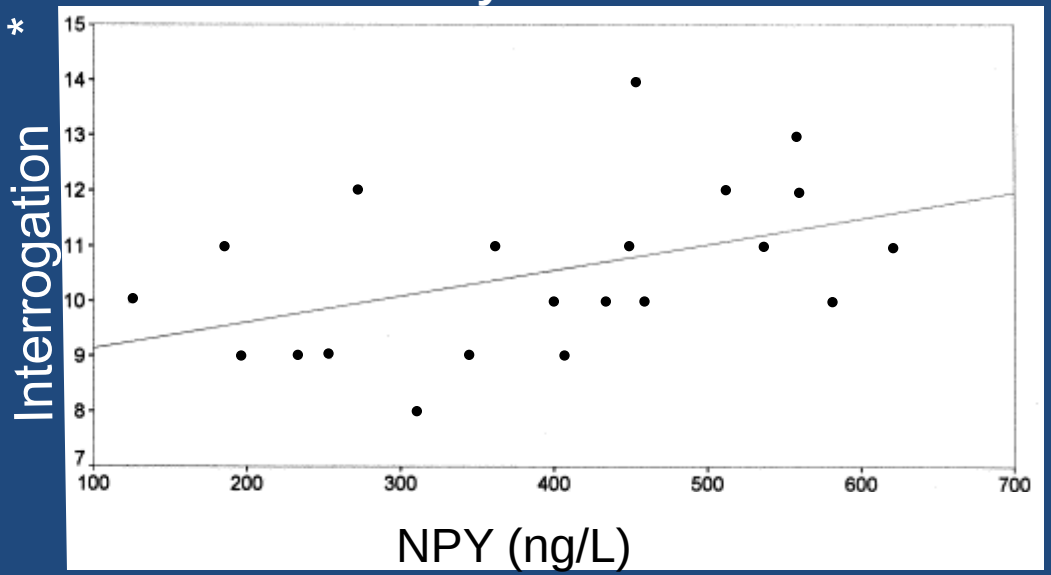

*Morgan et al (2002), Biol Psych, 52, 136.*

# DHEA(S)/Cortisol Ratio and Objective Military Performance

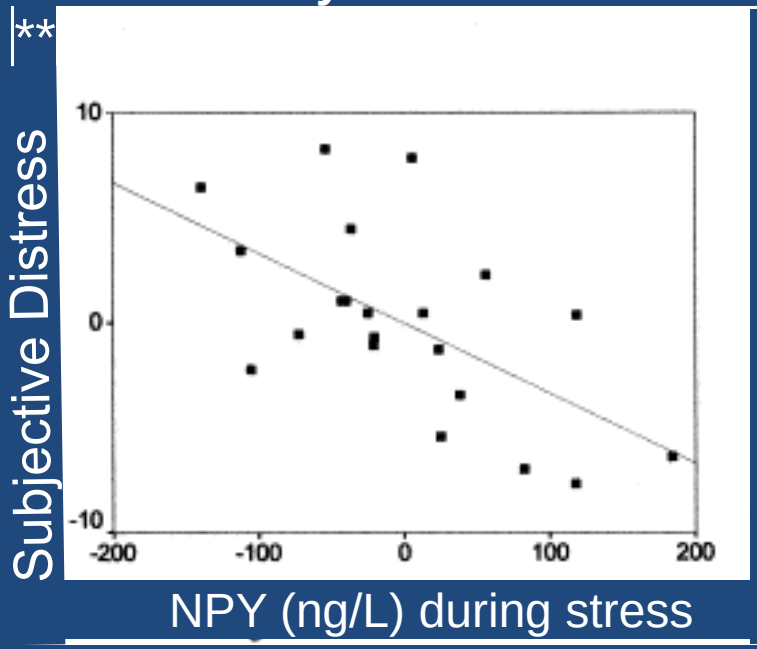


# Neurochemical Stress Response & Performance

## US Army SERE Course




## US Navy SEAL Survival School




** Morgan et al (2000), Biol Psych, 47, 902.*
*** Morgan et al (2002), Biol Psych, 52, 136.*

# Support for Involvement of Glutamate Decarboxylase 1 and Neuropeptide Y in Anxiety Susceptibility

**Genetic mapping efforts have identified putative susceptibility genes for human anxiety disorders. The most intensively studied genes are involved in neurotransmitter metabolism and signaling or stress response. In addition, neuropeptides and targets of anxiolytics have been examined. It has become apparent that gene environment interactions may explain individual variation in stress resilience and predisposition to mental disorders. We aimed to replicate previous genetic findings in 16 putative anxiety susceptibility genes and further test whether they modulate the risk for developing an anxiety disorder in adulthood after childhood stress exposure. We tested 93 single-nucleotide polymorphisms (SNPs) for genetic association to anxiety disorders in the Finnish population-based Health 2000 sample (282 cases and 575 matched controls). In addition, we examined by logistic regression modeling whether the SNP genotypes modified the effect of the number of self-reported childhood adversities on anxiety disorder risk. The most significant evidence for association was observed in glutamate decarboxylase 1 (GAD1) with phobias (P = 0.0005). A subsequent meta-analysis (N = 1985) incorporating previously published findings supported involvement of a single GAD1 risk haplotype in determining susceptibility to a broad range of internalizing disorders (P = 0.0009). We additionally found that SNPs and haplotypes in neuropeptide Y (NPY) modified the effect of childhood adversities on anxiety susceptibility (P = 0.003). In conclusion, we provide further support for involvement of mainly GAD1, but also NPY in determining predisposition to anxiety disorders.**

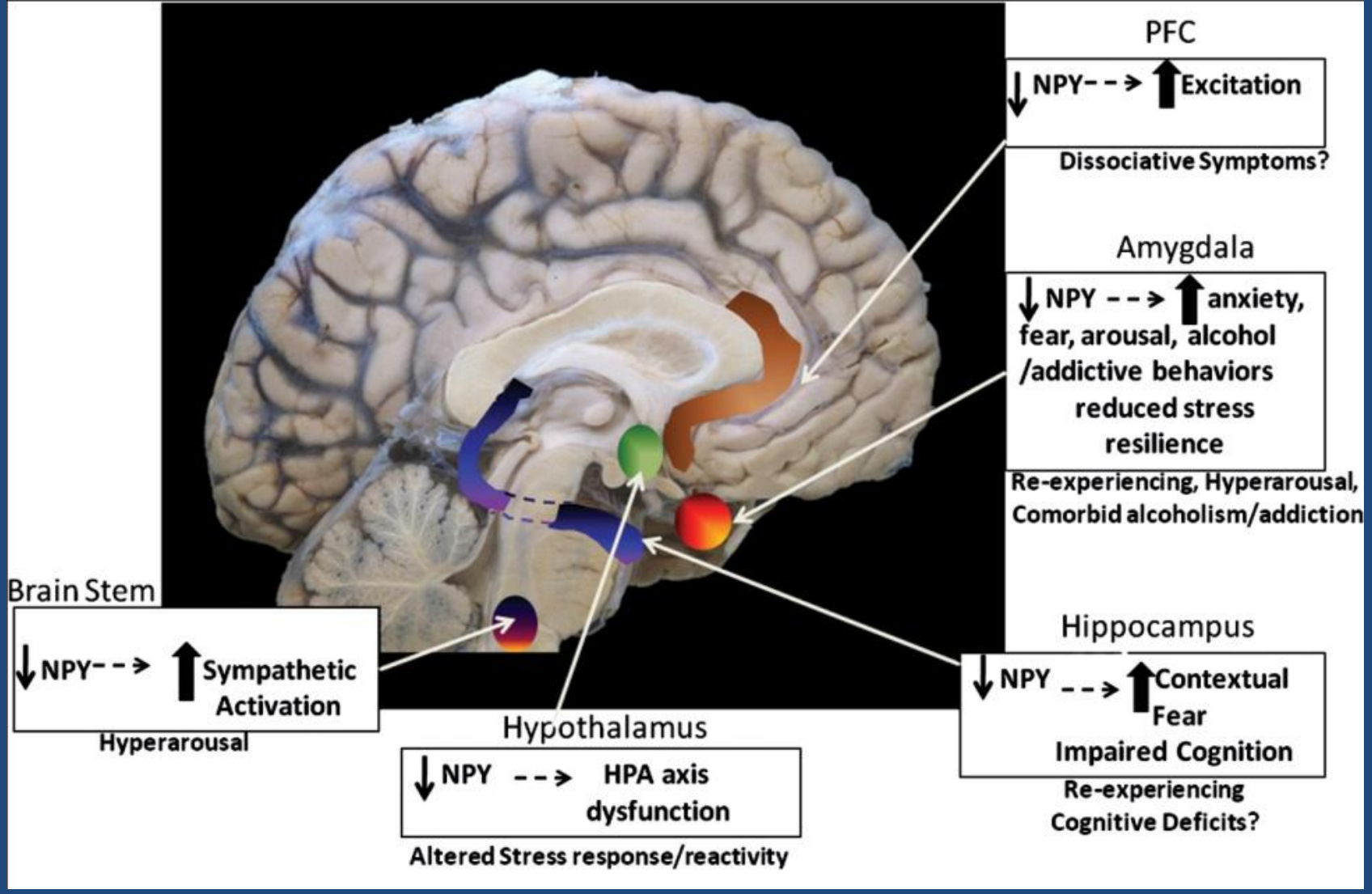
*Donner J, Sipilä T, Ripatti S, Kananen L, Chen X, Kendler KS, Lönnqvist J, Pirkola S, Hettema JM, Hovatta I. 2012. Am J Med Genet Part B 159B:316–327.*

# Emotion Processing, Major Depression, and Functional Genetic Variation of Neuropeptide Y

**Among healthy individuals, negatively valenced words activated the medial prefrontal cortex. Activation within this region was inversely related to genotype-predicted NPY expression (P = .03). Whole-brain regression of responses to negative words showed that the rostral anterior cingulate cortex activated in the low-expression group and deactivated in the high-expression group (P < .05). During the stress challenge, individuals with low-expression NPY genotypes reported more negative affective experience before and after pain (P = .002). Low-expression NPY genotypes were overrepresented in subjects with MDD after controlling for age and sex (P = .004). Population stratification did not account for the results.**

**These findings support a model in which NPY genetic variation predisposes certain individuals to low NPY expression, thereby increasing neural responsivity to negative stimuli within key affective circuit elements, including the medial prefrontal and anterior cingulate cortices. These genetically influenced neural response patterns appear to mediate risk for some forms of MDD.**

*Mickey BJ, Zhou Z, Heitzeg MM, Heinz E, Hodgkinson CA, Hsu DT, Langenecker SA, Love TM, Peciña M, Shafir T, Stohler CS, Goldman D, Zubieta J-K, Arch Gen Psychiatry. 2011 February;68(2):158-166*




Potential association of NPY to posttraumatic stress disorder pathophysiology: enduring deficits in NPY in various regions of the limbic brain can contribute to sensitized fear, anxiety, stress responses, arousal and cognitive deficits, based on preclinical evidence. NPY deficits in the brain stem may promote sympathetic overdrive. HPA, hypothalamic–pituitary–adrenal; PFC, prefrontal cortex; ↑, increase; ↓, decrease; ?, not clear at present.

*Sah R and Geracioti TD. Molecular Psychiatry* 18, 646-655; doi:10.1038/mp.2012.101

# Neuropeptide Y (NPY)

- 36 amino acids
- 4271.74 g/mol
- Lipophobic
- Biphasic half-lives
  - 4-5 min and 20-30 min
- NPY receptors
  - Y1, Y2, (Y3), Y4, Y5, y6

*Nature Vol. 296 15 April 1982*

8. Armstrong, C. M. *J. gen. Physiol.* **50,** 491–503 (1966).
9. Conti, F., DeFelice, L. J. & Wanke, E. *J. Physiol., Lond.* **248,** 45–82 (1975).
10. Hodgkin, A. L. & Huxley, A. F. *J. Physiol., Lond.* **117,** 449–472 (1952).
11. Almers, W. & Armstrong, C. M. *J. gen. Physiol.* **75,** 61–78 (1980).
12. Gilly, W. F. & Armstrong, C. M. *Biophys. J.* **29,** 485–492 (1980).
13. Conti, F. & Nehler, E. *Nature* **285,** 140–143 (1980).

**Neuropeptide Y—a novel brain peptide with structural similarities to peptide YY and pancreatic polypeptide**

**Kazuhiko Tatemoto, Mats Carlquist & Viktor Mutt**

Department of Biochemistry II, Nobel Medical Institute, Karolinska Institute, S-104 01 Stockholm, Sweden

# Delivering NPY to CNS

NPY → Blood-Brain Barrier (BBB) → Brain

cial conditions. This could explain why chronically disabling a gene or suppressing a protein's function often shows no obvious effects or an unexpected phenotype.



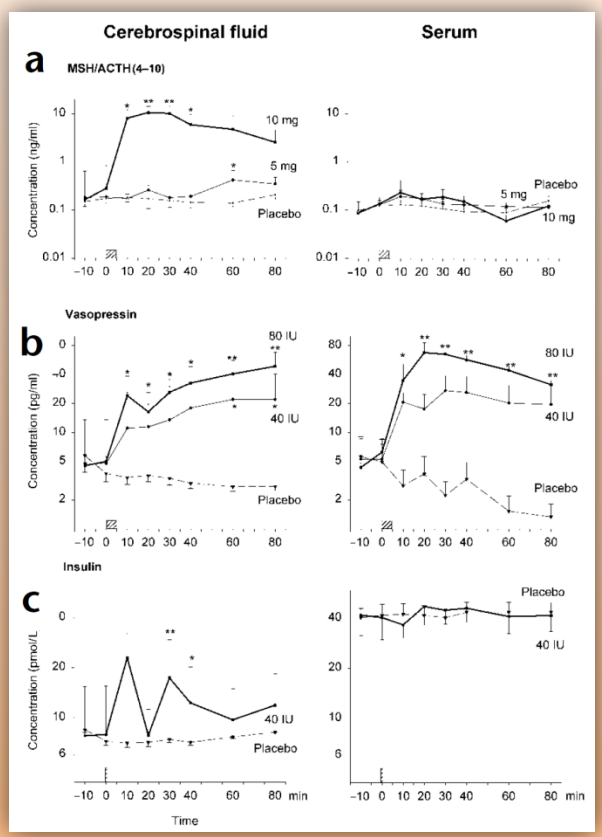
## Sniffing neuropeptides: a transnasal approach to the human brain

Jan Born[1], Tanja Lange[2], Werner Kern[2], Gerard P. McGregor[3], Ulrich Bickel[4] and Horst L. Fehm[2]

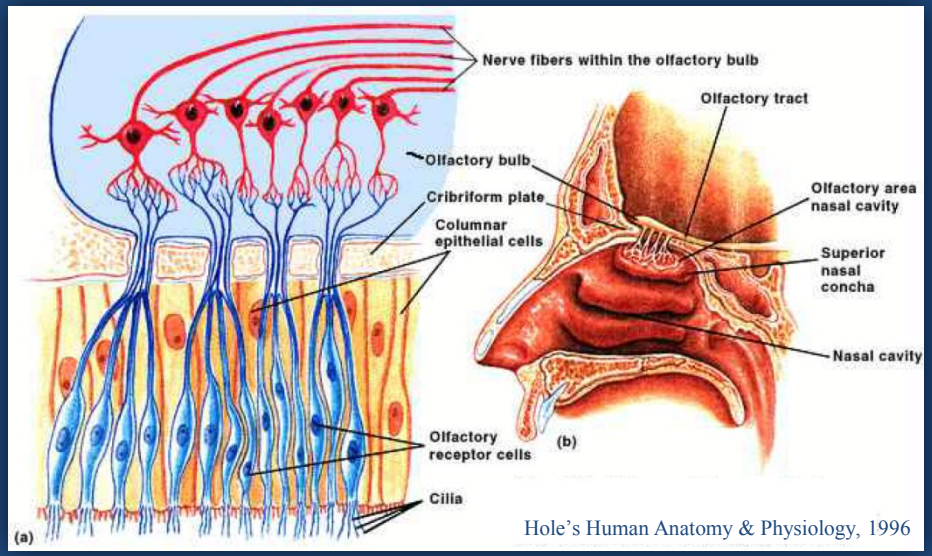
**Table 1. Accumulation of MSH/ACTH(4–10), vasopressin and insulin in CSF and blood serum.**

| | CSF Mean | CSF s.e.m. | CSF *P* | Serum Mean | Serum s.e.m. | Serum *P* |
|---|---|---|---|---|---|---|
| **MSH/ACTH(4–10)** | **AUC (ng/ml) × min** | | | **AUC (ng/ml) × min** | | |
| Placebo | 7.45 | 8.98 | | 8.80 | 1.41 | |
| MSH/ACTH(4–10), 5 mg | 21.53 | 7.11 | 0.30 | 10.91 | 0.26 | 0.48 |
| MSH/ACTH(4–10), 10 mg | 514.49 | 195.4 | 0.004 | 10.98 | 2.98 | 0.62 |
| **Vasopressin** | **AUC (pg/ml) × min** | | | **AUC (pg/ml) × min** | | |
| Placebo | 254.4 | 65.6 | | 207.4 | 202.0 | |
| Vasopressin, 40 IU | 1,319.1 | 821.8 | 0.05 | 1,674.0 | 931.8 | 0.14 |
| Vasopressin, 80 IU | 2,481.9 | 732.4 | 0.009 | 3,749.8 | 348.6 | 0.009 |
| **Insulin** | **AUC (pmol/l) × min** | | | **AUC (pmol/l) × min** | | |
| Placebo | 603.2 | 34.6 | | 3,410.5 | 106.1 | |
| Insulin, 40 IU | 1,091.1 | 219.8 | 0.028 | 3,414.3 | 276.8 | 0.22 |

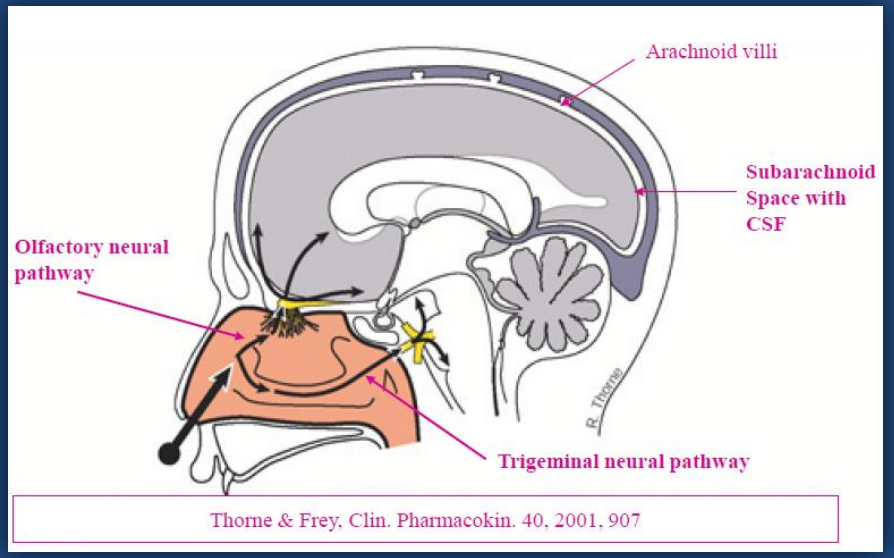
Concentrations of the peptides expressed as area under curve (AUC; using the trapezoid method) within 80 min after intranasal administration. $P < 0.05$ indicates significance in comparison with concentrations after placebo administration. Significance of accumulations was also confirmed in comparisons of average post-administration increases with pre-administration baseline concentrations.



# Nose-to-Brain Pathway

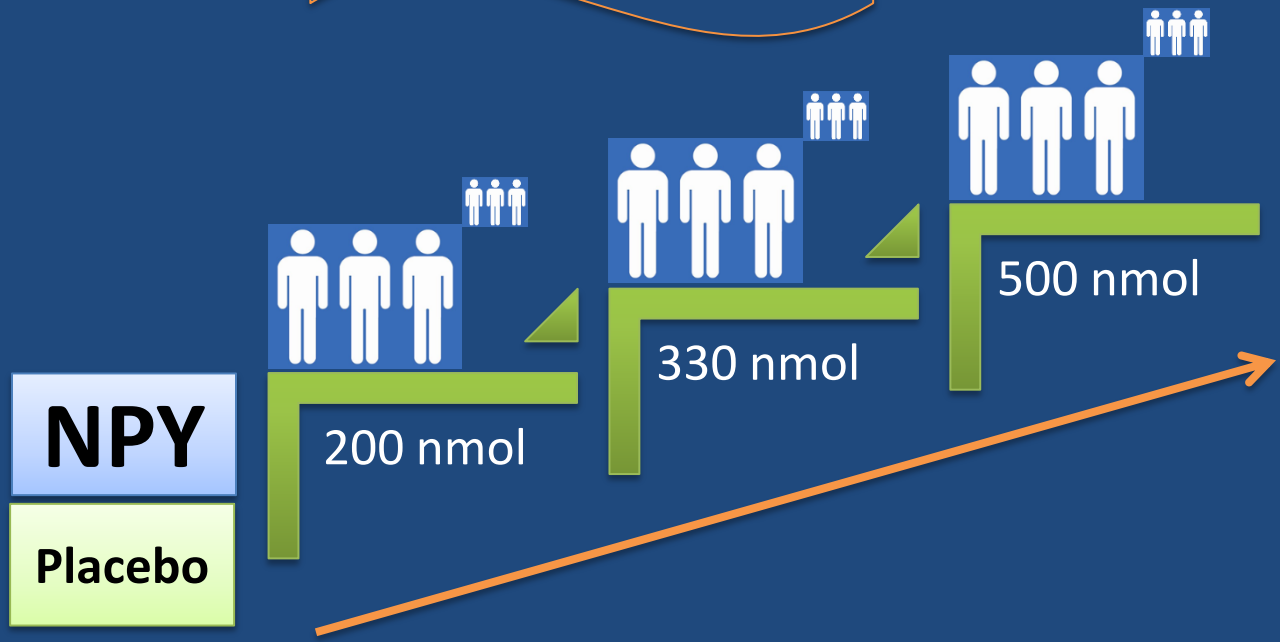


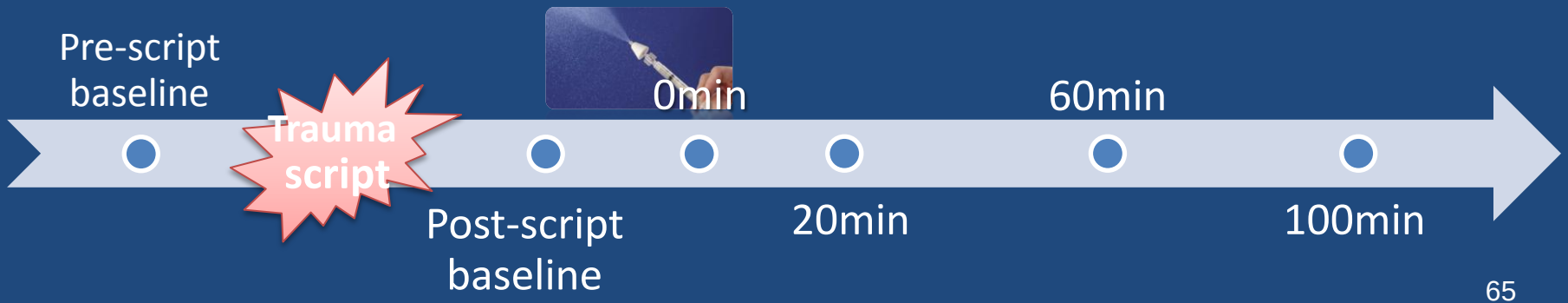
Hole's Human Anatomy & Physiology, 1996



Thorne & Frey, Clin. Pharmacokin. 40, 2001, 907

# Current Dose-Finding NPY Study



# Intranasal NPY in Rats

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Neuroscience. 2013 Apr 16;236:298-312. doi: 10.1016/j.neuroscience.2013.01.040. Epub 2013 Jan 30.

**Single intranasal neuropeptide Y infusion attenuates development of PTSD-like symptoms to traumatic stress in rats.**

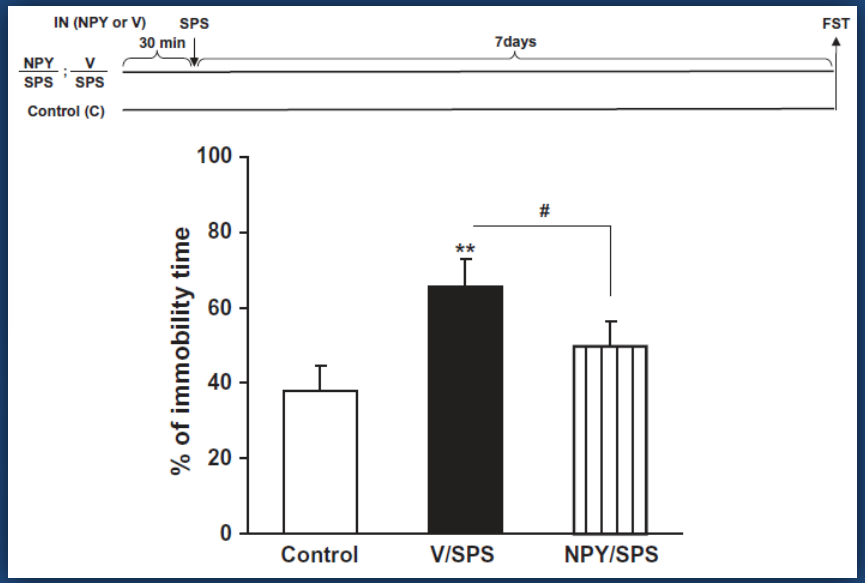
Serova LI, Tillinger A, Alaluf LG, Laukova M, Keegan K, Sabban EL.

Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla, NY 10595, USA.

**Table 1.** Concentration of NPY in CSF and plasma 30 min after IN NPY administration

| Treatments | CSF | Blood (ng/ml) |
|---|---|---|
| Water | Nd | 191 ± 30 |
| NPY, 50 µg | 0.4 ± 0.1 µg/ml | 211 ± 4.4 |
| NPY, 90 µg | 2.6 ± 0.27 µg/ml | 206 ± 6.2 |

Nd – not detectable.



# "Intranasal Neuropeptide Y Reverses Anxiety and Depressive-like Behavior Impaired by Single Prolonged Stress PTSD Model"

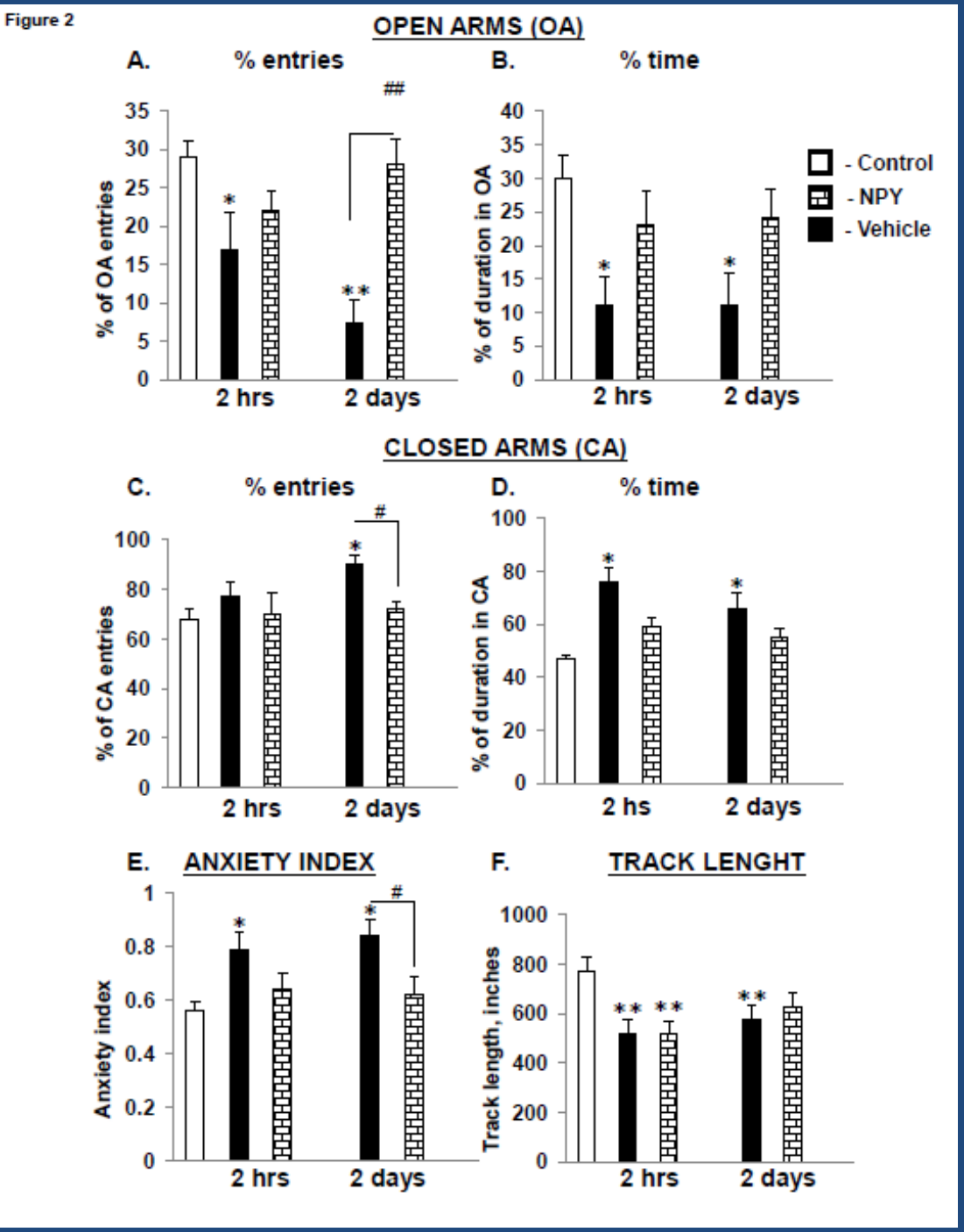
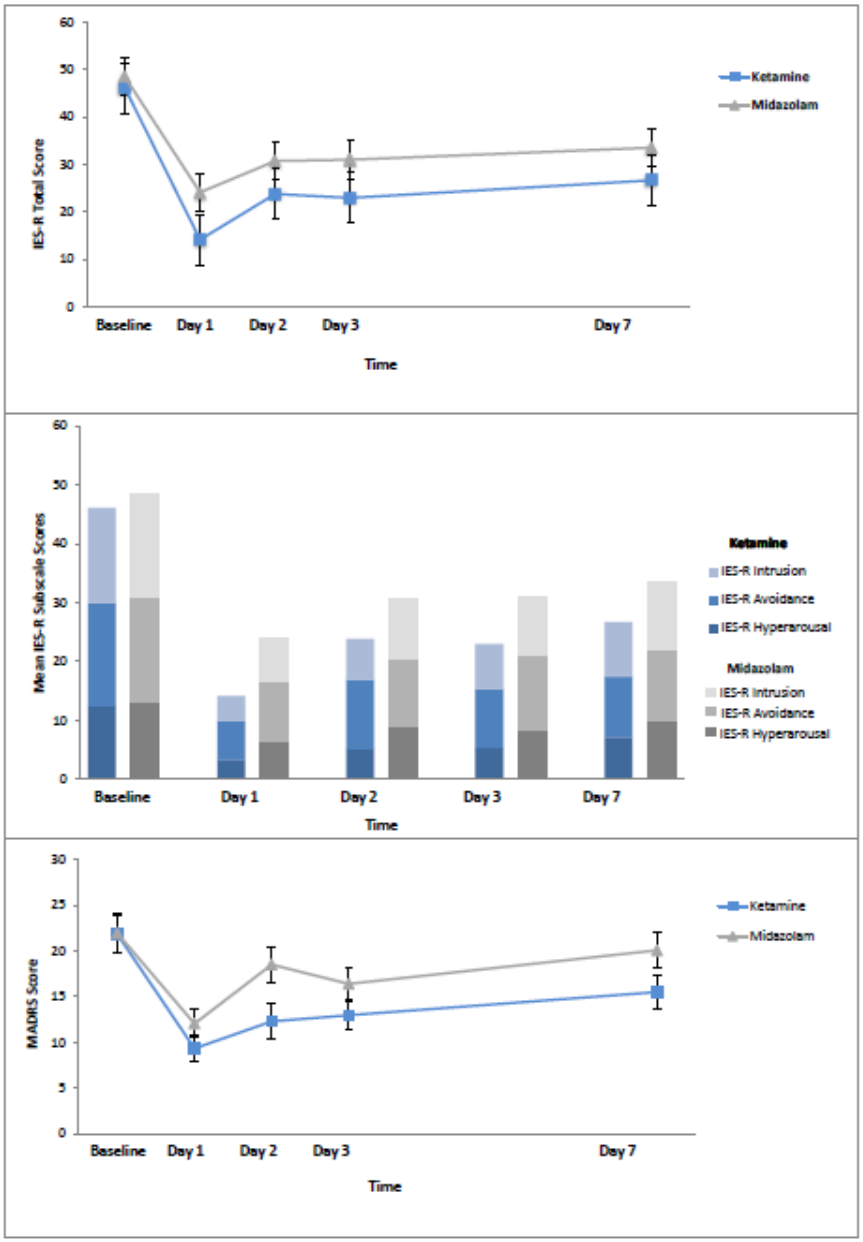



**Figure 2.** Effect of IN NPY administration on anxiety-like behavior impaired by SPS. **A.** open arm (OA) entries; **B.** OA time; **C.** closed arm (CA) entries; **D.** CA time; **E.** anxiety index; **F.** track length. Data are presented as mean ± SEM. *p ≤ 0.05, ** p ≤ 0.01 vs. Control; # < 0.05, ## < 0.01 vs. vehicle at same time. n=10 per group.

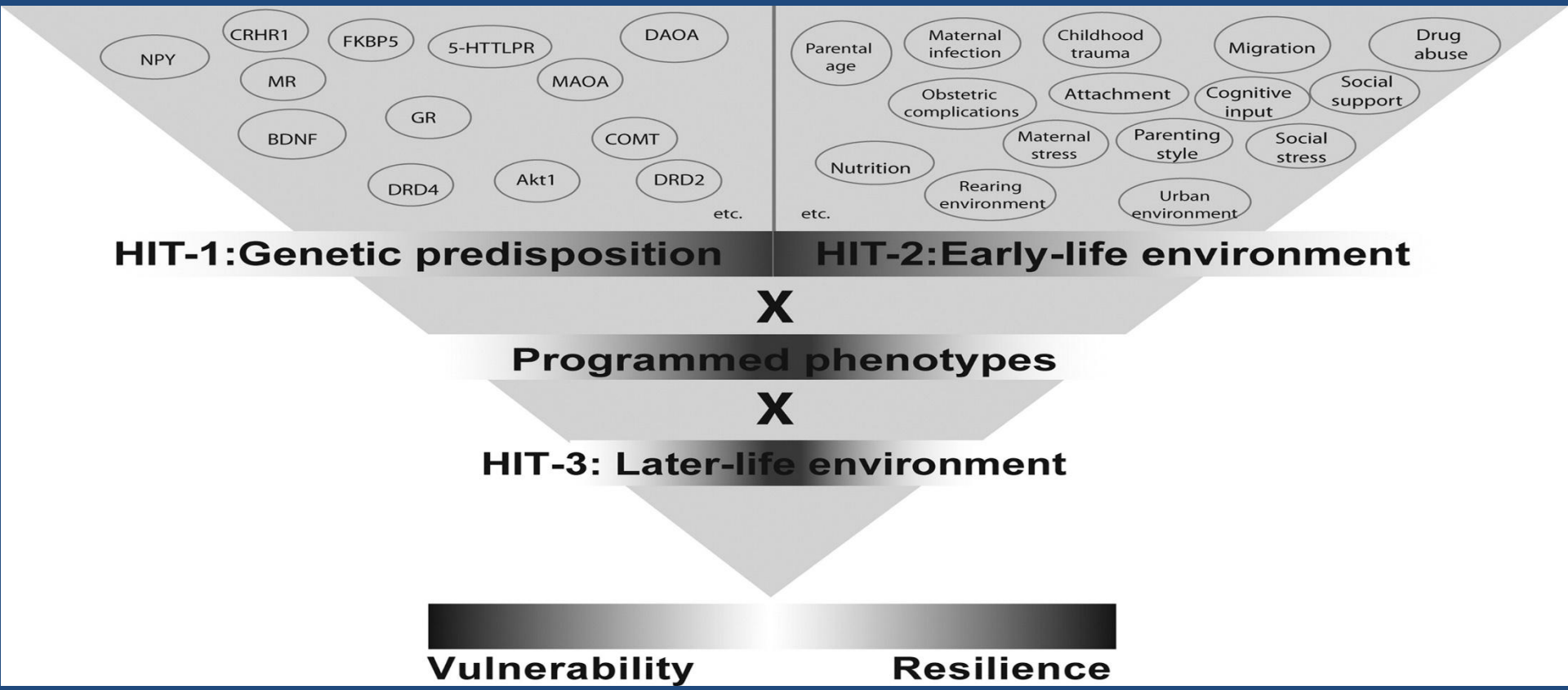
L.I. Serova, M Laukova, Alaluf and EL Sabban; Elsevier Neuropsychopharmacol. Submitted; Under Review

# Efficacy of Intravenous Ketamine in Chronic Posttraumatic Stress Disorder: A Randomized Controlled Trial




**Note:** Change in the Impact of Event Scale - Revised (IES-R) total score, the IES-R mean subscale scores, and the Montgomery-Asberg Depression Rating Scale (MADRS) score over 1 week for the first period (n = 41). Error bars represent standard errors.

Adriana Feder, Michael K. Parides, James W. Murrough, Andrew M. Perez, Julia E. Morgan; Shireen Saxena; Katherine Kirkwood, Marije aan Het Rot, Kyle A.B. Lapidus, Le-Ben Wan, Dan Iosifescu, Dennis S. Charney,; Submitted; Under Review

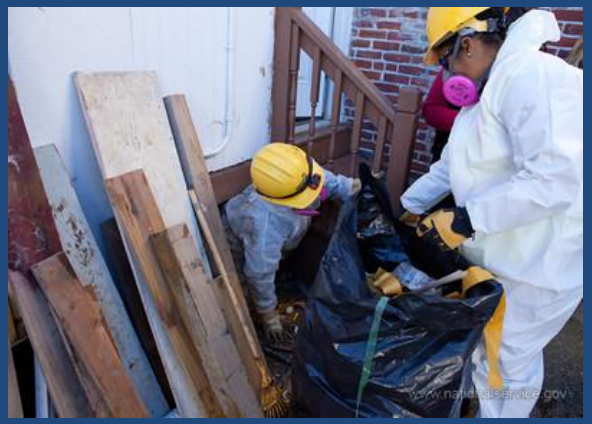



The three-hit concept of vulnerability and resilience. Multi-genic inputs (hit-1) interact with early-life environmental inputs and experience-related factors (hit-2), programming phenotypes with differential susceptibility to later-life challenges (hit-3). Depending on the interaction of "programmed phenotypes" with later-life environment vulnerability or resilience may precipitate. *Abbreviations*: *5-HTTLPR*, serotonin-transporter-linked polymorphic region; *Akt1*, RAC-alpha serine/threonine-protein kinase; *BDNF*, brain-derived neurotrophic factor; *COMT*, catechol-*O*-methyltransferase; CRHR1, corticotropin releasing hormone receptor 1; *DAOA*, d-amino acid oxidase activator; *DRD2*, dopamine receptor $D_2$; *DRD4*, dopamine receptor $D_4$; *FKBP5*, FK506 binding protein 5; *GR*, glucocorticoid receptor; *MAOA*, monoamine oxidase A; *MR*, mineralocorticoid receptor; *NPY*, neuropeptide Y.

Nikolaos P. Daskalakis , Rosemary C. Bagot , Karen J. Parker , Christiaan H. Vinkers , E.R. de Kloet
Psychoneuroendocrinology Volume 38, Issue 9 2013 1858 – 1873; http://dx.doi.org/10.1016/j.psyneuen.2013.06.008


28

# Superstorm Sandy's Survivors: New Jersey - Stronger than the Storm

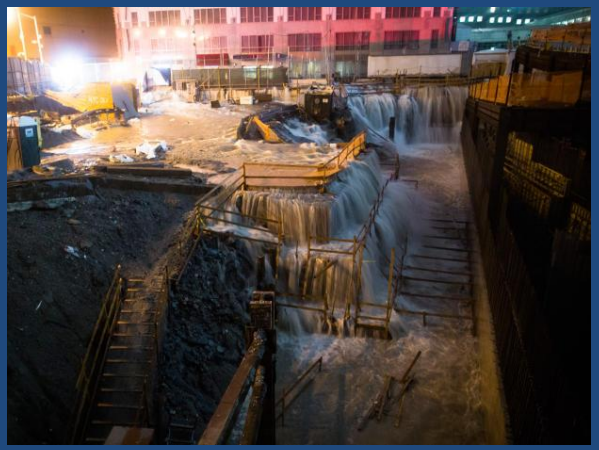




# Superstorm Sandy's Survivors: New York - Better Than Before

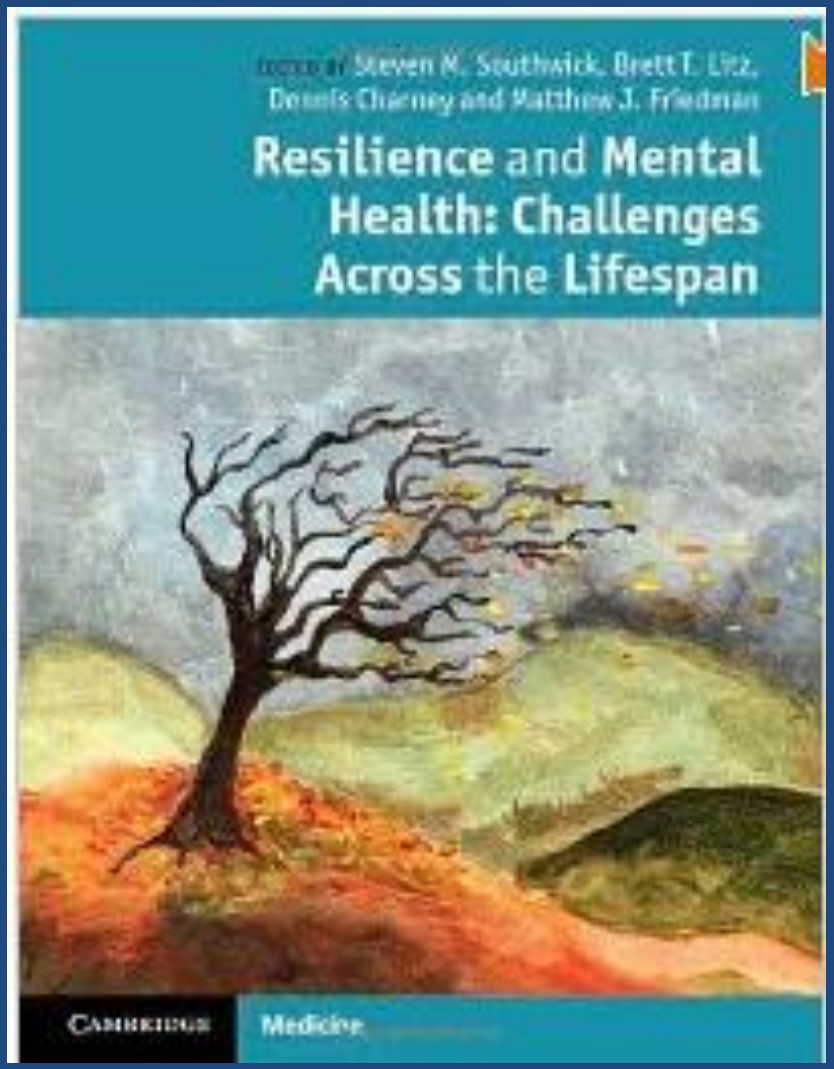


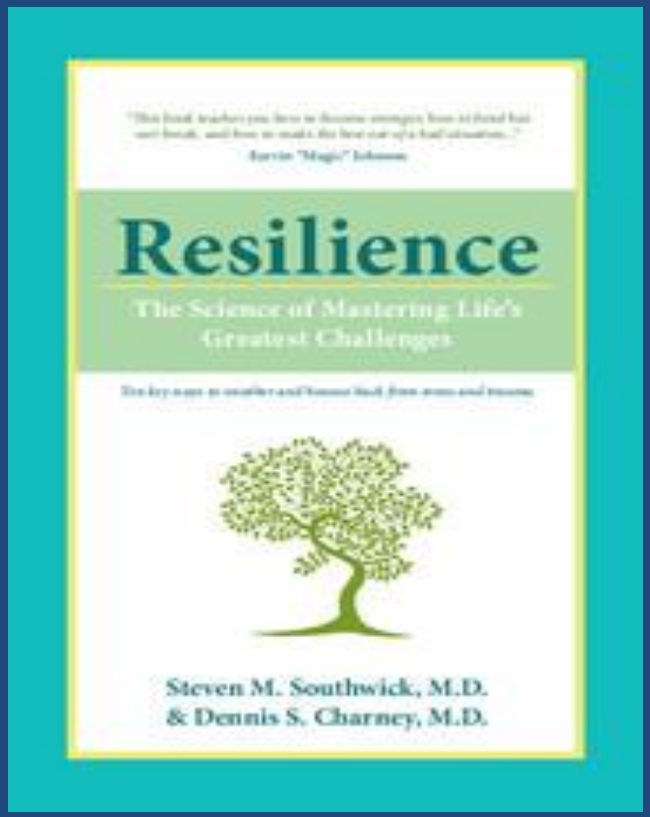






# Books




***Resilience: The Science of Mastering Life's Challenges***

**Steven M. Southwick, MD**
***With* Dennis S. Charney, MD**

Cambridge University Press 2012