

Department of Behavioral Sciences and Leadership

West Point Resilience Project (WPRP)

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Effects of Neuropeptide Y on Resilience to PTSD

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EFFECTS OF NEUROPEPTIDE Y ON RESILIENCE TO PTSD

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EFFECTS OF NEUROPEPTIDE Y ON RESILIENCE TO PTSD

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Introduction

The current war has once again highlighted the issue of posttraumatic stress disorder (PTSD). However, recent research indicates that experiencing a traumatic event does not necessarily mean that PTSD is the only possible outcome of war. Many Soldiers will actually be resilient under such circumstances as measured by circulating levels of neuropeptide Y (NPY). Increased levels of NPY are associated with reduced anxiety as well as better performance and memory (Sajdyk, 2008; Morgan et al., 2000; Charney, 2004). The current paper focuses on PTSD, resilience and physiological processes associated with each of these outcomes and how understanding these processes will allow for examining resilience in Soldiers who participate in the U.S. Army's Comprehensive Soldier Fitness program. This program is designed to improve readiness and performance along five dimensions of strength: physical, emotional, social, spiritual, and family that reflect resilience.

Resilience

Resilience has been defined as, "the general capacity for a flexible and resourceful adaptation to external and internal stressors" (Collins, 2007). It is a key characteristic in a person's ability to resolve both the day-to-day hassles and the traumatic, life-altering events people experience. The terrorist attacks on September 11, 2001 are unquestionably a traumatic experience that altered the lives of many. Bonanno et. al. (2006) found that 65.1% of a 2,752 person sample of those exposed to the attacks were resilient to the trauma they experienced that day. They did a further analysis to discover that even in the most extreme trauma exposure cases the prevalence of resilience did not drop below a third of the population. There is a large lesson to be taken away from this when analyzing this situation from a military perspective. Soldiers currently operating in the Middle East are continuously exposed to extreme traumatic situations

while performing combat operations. What can we learn from 9/11 that applies to our military forces?

In 2008, the Army implemented a program under Brigadier General Rhonda Cornum entitled Comprehensive Soldier Fitness (CSF). Their goal is to find the best way to promote resilience among Soldiers to PTSD, depression, and anxiety (Hames, 2009). The goal of this paper is to propose a method to supplement the CSF program in order to better screen soldiers for resilience so the Army can implement measures for Soldiers that are not resilient towards extreme stress and trauma. This paper will explain several major factors that contribute to resilience, PTSD, the cognitive and physiological responses to stress, and will outline a methodology of how to use neuropeptide Y (NPY) to screen for resilient individuals.

Recent literature proposes that common personality traits among resilient people generally include reflectiveness and positive responses to newly occurring situations (Collins, 2007). These two traits help individuals to “bounce back” and learn from stressful situations so they can deal with similar situations more efficiently in the future. Resilient people may often appear zestful and energetic and never seem disturbed by negative circumstances. They may appear to have an extraordinary amount of resilient strength that is not attainable to the average person. Collins (2007) states that this is a very common misperception of people with high resilience. Resilient people also experience negative emotions and are deeply moved by dynamic events, but the difference is that they do not become overwhelmed by their emotions. Instead, they are better able to learn new skills from life experiences which enable them to be better able to handle future stresses. Additionally, resilient people feel a sense of pride in their work and use positive emotions to cope with stresses.

Positive emotions and optimistic disposition are perhaps some of the most common traits resilient people use to cope with stress. Positive emotion acts as a buffer against stress to allow the body to replenish and restore itself to effectively implement good coping mechanisms for future stressors (Ong, Bergman, Bisconti, & Wallace, 2006). It follows the logic of the “Broaden and Build” theory in which positive emotions provide a temporary broadening of one’s perception of a situation to allow them more flexibility to perceive a stressor differently and potentially increase their overall well-being and resilience (Tugade et. al., 2004). Having an optimistic disposition helps individuals use positive emotions as a “psychological breather” that helps to prevent becoming overwhelmed with negative thoughts and appraisals. This in turn helps to sustain better self-esteem and a feeling of effectiveness which ultimately helps to restore a person’s sense of worth and feeling that they are cared about (Collins, 2007).

Baldwin, Kennedy, and Armata (2008) studied 37 mothers with regard to the stresses they incurred on a daily basis and the distress level they perceived based on their level of resilience and dispositional optimism. They found that people with higher resilience and optimism experienced less distress but were unable to connect this finding to the concentration of secretory immunoglobulin A, which is an antibody that acts as the immune systems first line of defense to respiratory illnesses. However, they were able to determine that optimism was negatively correlated to distress levels and that optimism promoted active coping strategies.

In a study of 272 Operation Iraqi Freedom and Operation Enduring Freedom Connecticut National Guard Soldiers they too found that resilient individuals used active and positive coping strategies (Pietrzak, Johnson, Goldstein, Malley & Southwick, 2009). The Soldiers answered approximately 200 questions via multiple surveys like the Connor-Davidson Resilience Scale (CD-RISC), the Combat Experiences Scale (CES), and the Unit Support Scale (USS). The

authors found that positive factors of social support, hardiness, perceived support and perception of worth and helpfulness were significant indicators of resilience. The importance of social support was further substantiated in Maguen's et. al. (2005) study of Gulf War I veterans. The findings indicate that social support after a deployment is a significant indicator of posttraumatic growth and resilience. Resilience is extremely important in preventing depression, anxiety and PTSD as it enables an individual to bounce back from traumatic events and apply active and positive coping strategies.

PTSD

PTSD is described as, "A syndrome of emotional and behavioral disturbance following exposure to a traumatic stressor that injures or threatens self or others, and that involves the experience of intense fear, helplessness, or horror" with symptoms of: anxiety, continuous alertness and arousal, irritability, avoidance and denial, repeated nightmares, impaired concentration, acting out, and withdrawal (Miller, 1999). PTSD is an extremely serious condition that can drastically reduce the effectiveness of an individual. To make it worse, in the Army there is a common stereotype that if a Soldier seeks help, then that Soldier is weak, broken, or ineffective. Obviously no Soldier wants to be labeled like this, so Soldiers may likely keep emotional troubles to themselves and let their anxiety and fears build up to the point that they are forced to see a professional.

Kilner (2005) argues that the Army misses a major issue in combating PTSD and promoting resilience in Soldiers. Soldiers often execute missions with little information as to what the actual purpose of what they are doing is. They don't know the "big picture" so it is harder for them to justify their actions and feel that their job is worthwhile (a key component of resilience as stated above). Additionally, leaders generally only focus on the experiences that

happen to the Soldier and seldom on a Soldier's actions (i.e. killing). Taking another human's life is rarely covered in Army teachings and it is unnatural for a human to do. An Army Chaplain deployed to Mosul, Iraq said he counseled Soldiers who often asked him questions like "Did I commit murder?" or "Is God going to forgive me?" or "How am I going to be when I get back home?" Having a Soldier ask these questions is extremely concerning and a leader must do something about it, but the problem continues further. Soldiers typically claim that since psychiatrists aren't on the front lines, psychiatrists "don't understand" what it is like to kill someone and Soldiers don't feel comfortable talking about it. This is certainly not healthy as the probability of developing PTSD increases by 42% when a Soldier experiences an atrocity (Kilner, 2005).

An investigation of PTSD among Soldiers involved in peace keeping missions in Somalia demonstrates the "snowballing" effect of untreated PTSD. Within one year of returning to the United States 460 Soldiers completed a questionnaire asking them their level of combat exposure by rating it on a 5 point Likert-like scale (0-4) and were then interviewed via telephone 21 months later and asked to rate their combat exposure on the War-zone Exposure Scale (WZES). While there was a correlation of .66 between the two time periods, exposure ratings increased from 1.88 at time one to 2.23 at time 2. This "exaggeration" of combat exposure correlated to increased reports of stressor frequency, meaning resilience is decreasing as time elapses due to untreated PTSD symptoms.

Stress

As we know there is both good and bad stress. Good stress, or eustress, challenges and motivates us to accomplish what we normally might not be able to. Bad stress, or distress, threatens us through fear of harm, danger or is simply irritating. A large number of factors affect

our stress level, ranging from sleep quality, to diet and exercise, to social interactions. We have programmed stress mediators in our automatic, neuroendocrine, and immune systems that help to regulate levels of neurotransmitters and hormones in our bodies (Selye, 1998). These systems are also subject to the influence of the prefrontal cortex which is often deemed the “thinking” region of the brain that can usually override actions (Henry, 1992). Understanding how we cope with the ever-varying stresses of our lives plays a key part in understanding resilience.

Allostasis is the process by which our body maintains balance amongst stressors as it constantly adjusts to maintain a healthy state necessary for survival (e.g., pH levels, body temperature) by achieving stability through change. Our body is programmed to adapt to manageable stress on a day-to-day basis, but also has “emergency” capabilities to mobilize energy, enhance memory and activate the immune system when allostatic overload occurs, or your body is “stressed out” (McEwen, 2006). In this state the body and mind are in a state of constant anxiety, frustration, fear, fatigue, and a person may feel a general lack of control over their situation. To make the situation worse, when this occurs people sometimes turn to maladaptive coping strategies that hurt the body more than help. Drug and alcohol use, sleepless nights and overeating turn from a “simple one time fix” to chronic bad habits that give the body no time to recover. These behaviors may be indicative of type 2 allostatic overload in which social conflict occurs but it does not trigger an emergency state of mind. Type 2 overload can only be counterbalanced through learning or a change to an individual’s social structure (McEwen & Wingfield, 2003).

A key system in the regulation of extreme stress is the hypothalamic-pituitary-adrenal axis (HPA axis). Over activation of the HPA axis has severe effects on both cognitive and physiological processes. Overstimulation is often the result of prolonged and untreated traumatic

stress that places the body in a constant state of alertness and anxiety due to elevated and unbalanced cortisol levels that decrease plasticity and growth in the brain (Yehuda, 2002).

Common remedies to ameliorate elevated stress levels are exercise and social support. Exercise stimulates neurogenesis and increases levels of brain-derived neurotrophic factor (BDNF), a protein known to enhance the growth of brain cells and overall cell survival, especially in the hippocampus. This in turn could help to reduce allostatic load because the hippocampus is responsible for working memory (Cotman & Berchtold, 2002). In short, if the brain can store more working memory, it will be better able to connect key components of problems to solve problems and stressors more readily. Social support was the best predictor of a Soldier's ability to promote posttraumatic growth (PTG) in a study of Gulf War I veterans. Of note, the study found that post-deployment support was a significant predictor of PTG (Maguen et al., 2005). This means that when a Soldier returns from deployment it is essential for them to establish a strong support network (if not already there). PTG is essential to learning from past experiences so Soldiers are able to cope with future burdensome allostatic loads.

Locus Coeruleus

Having already discussed behavioral resilience to stress above, one must also understand biological resilience to stress and the biological mechanics behind what can cause stress-related damage to the brain. When a human being encounters something that it perceives as a threat, we enter into what is known as the “fight-or-flight” response. In this response, our body is physically prepared to defend or flee, depending on the level of threat perceived. Our body physically shuts down all functions not essential to these two tasks. As such, functions, such as digestion, cease, and vital functions, such as heart rate, increase. This prepares the body to execute quick, decisive moments, priming all available resources (Charney, 2004). This all

happens in a matter of minutes, instantaneously one's brain initiates a chemical process that prepares the body. The first step in this process occurs in one's sensory neurons. Once your senses, such as sight, smell, or sound, perceive a threat, they send sensory motor signals along neurons to the brain. Here, it is passed from the sensory cortex to the hypothalamus, then routed to the brain stem. It is there that "fight-or-flight" processing begins, in an area of the brain known as the locus coeruleus. This neuro-electrical signal stimulates the locus coeruleus to release a chemical known as norepinephrine. This primes the brain, making a person more alert and attentive to the situation around them. This release of norepinephrine also controls the levels of responsiveness a person feels, which is directly tied to how much a stressor is perceived as a threat, and thus how quickly the locus coeruleus fires, discharging norepinephrine into the brain. This release of norepinephrine inhibits the function of higher level cognitive processes in the pre-frontal cortex. This forces the brain to rely on purely instinctual responses during "fight-or-flight" periods in the brain (Haas, 1989). Evolved over millions of years, these stress reactions take place in some of the oldest parts of the mammalian brain. All of these responses to stress are necessary for a human to be able to survive, especially in a combat environment. However, in situations such as combat, where stressors can be constant and persistent, the locus coeruleus can continually fire. Due to the locus coeruleus' feedback loops, including the interaction between the amygdala and the hypothalamus, the brain can sustain continuously high levels of norepinephrine. This results in huge amounts of norepinephrine in the brain, leading to chronic anxiety, fear, and intrusive memories. These continual hyperresponsive reactions to stress can contribute to post-traumatic stress disorder and depression (Feder, 2009).

Corticotropin-Releasing Hormone

At the same time the locus coeruleus activates, a second stress response system in the brain can be activated. This is known as the hypothalamic-pituitary-adrenal axis. Once the same sensory information that activated the locus coeruleus reaches the hypothalamus, the process begins. The electrical signal passed by the senses causes the hypothalamus to release an all important biochemical known as corticotropin-releasing hormone, or CRH. CRH is a chemical that once released, stimulates the pituitary gland, which in turn, then causes it to release a hormone signal telling the adrenal glands to release cortisol. Cortisol is the chemical directly tied to preparing the body for “fight-or-flight” by activating certain systems, while shutting down other non-essential ones (Bremner et al., 1997). However, CRH is also tied to many other important systems in the brain. CRH-containing neurons are found throughout the brain, on such areas as the central nucleus of the amygdala and the locus coeruleus. As more CRH is released by the hypothalamus, the receptor neurons in the amygdala are activated, causing an increase in fear-related behaviors. In a state of constant stress, the hypothalamus can be continually stimulated, resulting in a continual release of CRH. This leads to constant feelings of fear and decreased expectations of reward (Charney, 2004). As an added effect, the locus coeruleus also has CRH receptors, leading to increased activity as CRH levels increase. As such, when stressed, the locus coeruleus is further stimulated by CRH levels, increasing its firing rate and increasing the level of norepinephrine in the brain. In a chronic stress situation, these two related systems can leave an individual hyperresponsive, over-stressed, and with increased feelings of fear (Bremner et al., 1997). It is this system that is believed by researchers to play a major role in developing PTSD.

Neuropeptide Y

With a basic understanding of the biological basis for PTSD, a researcher can then examine the opposite concept, biological resilience. One of the leading candidates in resilience research is known as neuropeptide Y, or NPY. NPY is a 36 amino acid peptide which is found throughout the mammalian brain, and is involved in regulating food intake and fat processing storage in addition to its role in resilience. Receptors for NPY are associated with three key locations in the brain that deal with stress: the amygdala, the hippocampus, and the locus coeruleus. In the amygdala, increased NPY levels may be associated with decreased feelings of anxiety (Sajdyk, 2008). Increased levels of NPY is also associated with decreased memory retention in rats involved in foot-shock avoidance testing (Charney, 2004). In addition, NPY levels may also decrease the rate of locus coeruleus firing, resulting in lower levels of norepinephrine in the brain, which can lead to decreased chances of the brain sustaining prolonged damage due to constant stress (Morgan, 2002). Probably the most important function of neuropeptide Y, though, comes in its interaction with CRH. As stated above, CRH receptors are found throughout the brain, in areas specifically associated with stress reactions, such as the amygdala and the locus coeruleus. On both of these brain structures, NPY and CRH have counterbalancing functional effects. In the amygdala, CRH can promote activation, resulting in stimulation and increased feelings of anxiety, while NPY results in decreased amygdala arousal, and anti-anxiety feelings. In the locus coeruleus, CRH causes an increase in firing rate, increasing norepinephrine levels, while NPY has a counter effect, resulting in decreases in rate and level (Gutman, 2008). As such, researchers propose that ideal human brain would be the perfect balance of these two biochemicals. This is because CRH is needed to maintain the

adequate response to stress, allowing the human to fully prepare for “fight-or-flight,” while NPY is needed to counteract long term damage caused by prolonged stress.

Research consistently shows that those with PTSD exhibit lower concentrations of neuropeptide Y than those without. One study conducted by Sah, et al. (2009) at the University of Cincinnati, examined ten males with chronic combat-related PTSD versus 13 “healthy” male participants. The research team drew cerebrospinal fluid from participants in the morning, when neurochemicals are at their highest levels. From this, the team found that participants with PTSD had an average of 233.6 pg/ml, while the “healthy” control participants had an average of almost 360.0 pg/ml. Even after adjusting the data for age and body mass index, these researchers found evidence to suggest that PTSD sufferers’ NPY levels were significantly lower. This is important not only because it allows one to see a potential cause of PTSD, but it also shows that higher levels of NPY can quantifiably show that the concept of resilience exists.

In a related study conducted by the National Center for PTSD and Research, Morgan, et al. (2000), conducted research on seventy US Army Soldiers attending Survive Evade Resist Escape (SERE) School. These researchers collected two distinct sets of labs, the first group had their plasma NPY levels drawn prior to training (as a baseline), then 24 hours after concluding training. The second group had their plasma NPY levels drawn during the POW phase of the training, as well as the initial baseline. In addition to these two groups, the researchers also examined the difference between Special Forces Soldiers and those Soldiers completing the training from the regular Army. The findings showed a significant positive correlation between NPY levels and performance during interrogations. In addition, those with higher NPY levels showed were better able to remain focused on the situation at hand, while those who had lower levels of NPY, reported feelings of dissociation and helplessness. In addition, Special Forces

Soldiers, who through prior research display much lower rates of PTSD proportionally among their units, also displayed an ability to more quickly recover from stress depletion of NPY. Following training, 24 hours after completion, Special Forces Soldiers on average showed a return to baseline levels of NPY, while regular Army Soldiers still showed greatly depleted levels (Morgan et al., 2000).

A third study examined three populations: 11 Soldiers who were not exposed to combat, 11 combat exposed veteran's who did not display PTSD, and 12 combat veterans who displayed PTSD. This study found that the group of veterans who were exposed to combat but did not display current signs of PTSD had significantly higher levels of NPY, and that non-exposed and PTSD sufferers had comparable levels of NPY. This just further illustrates the idea that NPY can provide a biological mechanism for resilience to stress. In addition, this study also demonstrated a new concept for NPY. Among those Soldiers with the highest levels of NPY were those who were former sufferers of PTSD, but after more combat exposure, displayed no signs or symptoms (Yehuda et al., 2006). This is important because it illustrates the therapeutic effect NPY may have on those already suffering from PTSD.

Therapeutic Neuropeptide Y

In many recent studies, researchers have examined the biological effect of microinjecting NPY into the basolateral nucleus of the amygdala. One such study displayed two prominent results. First, researchers discovered that injecting rats with small amounts of NPY directly into the basolateral nucleus of the amygdala resulted in an immediate increase in resilient behaviors in rats receiving the treatment as opposed to the control rats (Sajdyk, et al., 2008). In addition, they found these resilient behaviors to last as long as eight weeks following the administration of the NPY injection. This led researchers to believe that injection of NPY was a valid option for

increasing resilience. In order to test its effect on rats already damaged by prolonged stress, the researchers first exposed the rats to prolonged stress, in order to over stimulate the CRH receptors and the locus coeruleus in the brain. They then injected small amounts of NPY into the amygdala, then compared the results to those of both baseline control rats and injected non-stressed rats. They found that, while the rats still displayed some symptoms of negative stress reactions, they were much less severe, almost on par with a baseline rat exposed to no stress (Sajdyk et al, 2008). This shows that resilience may actually be tied to brain plasticity, as inducing NPY into the stress-damaged systems of the brain may increase the plasticity of the brain, making it easier for one to adapt to stress.

Proposed Study Method

Based on the literature, NPY is a promising measure for testing Soldier resilience and may be incorporated into the Comprehensive Soldier Fitness program discussed above. If the Army is able to predict which Soldiers are more resilient to stress, then it can also then determine on which Soldiers to focus its interventions.

Participants

As part of CSF, eight brigades of the Army are part of the different intervention levels. One hundred Soldiers, a small number from each of these units, would be tested for NPY levels.

Apparatus and Procedure

Neuropeptide Y is fairly simple to collect from the human body. The researcher must collect a blood sample, and then use a centrifuge to spin off the plasma. Kits may be obtained from various companies. This test typically runs about fifty to one hundred dollars per test. Upon entrance to basic training, all recruits are required to provide a blood sample to test for HIV. At this same time, an NPY baseline level test could be performed, and entered into a

database. This would allow researchers to track whether those with higher natural levels of NPY were less susceptible to PTSD and other negative stress reactions. This group proposes that prior to deployment, at mid-tour leave, and a short time period post-deployment, that the Soldiers are tested for NPY levels. In doing so, it would allow CSF personnel to see exactly how their interventions are affecting the biological levels of resilience in Soldiers and if CSF trained Soldiers are more resilient. Data from CSF trained Soldiers may then be compared to data collected from recruits entering in at basic training to see if trends in either resilience or PTSD emerge. In addition, as research continues to progress, NPY may soon be an option as either a treatment for PTSD or as a way to psychologically prepare Soldiers for stress in combat.

Annotated References

Baldwin, D. R., Kennedy, D. L., & Armata, P. (2008). Short communication: De-stressing mommy: Ameliorative association with dispositional optimism and resiliency. *Stress and Health, 24*, 393-400.

A study of 37 mothers, the stress they incurred on a daily basis, and the distress they perceived based on their level of resilience and dispositional optimism. They found that people with higher resilience and optimism experienced less distress, but were unable to connect this finding to the concentration of secretory immunoglobulin A (S-IgA). S-IgA is an antibody that provides the immune system's first line of defense on mucosal surfaces and respiratory tract infections.

Bonanno, G. A., Galea, S., Bucciarelli, A., & Vlahov, D. (2006). Psychological resilience after disaster: New York city in the aftermath of the September 11th terrorist attack. *Psychological Science, 17*(3), 181-186.

The authors suggest that resilience to traumatic symptoms is actually higher than previously believed. They found that 65.1% of their 2,752 person sample involved in the 9/11 attacks were resilient and that even in people exposed to the extreme levels stress the resilience level did not drop below one third of the population. The authors suggest that people cope with traumatic events like 9/11 and grow from them psychologically.

Bremner, J.D. et al. (1997). Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *The American Journal of Psychiatry, 154*, 624-629.

Higher CSF CRF concentrations in patients with PTSD may reflect alterations in stress-related neurotransmitter systems. The higher CSF CRF concentrations may play a role in disturbances of arousal in patients with PTSD.

Charney, D. S. (2004). Psychological mechanisms of resilience and vulnerability. *American Journal of Psychiatry, 161*, 368-391.

Neuropeptide Y counteracts the effects of corticotropin releasing hormones (CRH) which is responsible for activating fear behavior. Chronic high levels of CRH may predispose individuals to PTSD and major symptoms of depression, anxiety, and fear. NPY additionally reduces the firing rate of the locus coeruleus which decreases the level of norepinephrine in the brain. This prevents overstimulation of responses like "fight or flight" and anxiety.

Collins, S. (2007). Social workers, resilience, positive emotions and optimism. *Practice: Social Work in Action*, 19(4), 255-269.

Focuses on the effects of positive coping mechanisms, in particular, positive appraisal, goal directed work, and finding the meaning and worth of everyday events. The author found that resilience, positive emotions and optimism are especially important in the daily work of a social worker's unrelenting job.

Cotman, C. W., & Berchtold, N. C. (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends in Neurosciences*, 25(6), 295-301.

Exercise stimulates neurogenesis and increases levels of brain-derived neurotrophic factor (BDNF), a protein known to enhance the growth of brain cells and overall cell survival, especially in the hippocampus. This in turn could help to reduce allostatic load because the hippocampus is responsible for working memory. In short, if the brain can store more working memory, it will be better able to connect key components of problems to solve problems and stressors more readily.

Feder, A. et al. (2009). Psychobiology and molecular genetics of resilience. *Nature Reviews Neuroscience*, (10), 446-457.

Every individual experiences stressful life events. In some cases acute or chronic stress leads to depression and other psychiatric disorders, but most people are resilient to such effects. Recent research has begun to identify the environmental, genetic, epigenetic and neural mechanisms that underlie resilience, and shows that resilience is mediated by adaptive changes in several neural circuits involving numerous neurotransmitter and molecular pathways. These changes shape the functioning of the neural circuits that regulate reward, fear, emotion reactivity and social behavior, which together are thought to mediate successful coping with stress.

Gutman, A.R. et al. (2008) The role of neuropeptide Y in the expression and extinction of fear-potentiated startle. *The Journal of Neuroscience*, 28(48), 12682-12690.

Neuropeptides are a promising target for novel treatments for anxiety and other psychiatric disorders and neuropeptide Y (NPY) has emerged as a key component of anxiolytic circuits in the brain. For this reason, we have evaluated the role of NPY in the expression and extinction of conditioned fear. We found that intracerebroventricular administration of NPY inhibits both baseline acoustic startle and the expression of fear-potentiated startle.

Haas, G. (1989). Neuropeptide Y-induced effects on hypothalamic corticotropin-releasing factor content and release are dependent on noradrenergic/adrenergic neurotransmission. *Brain Research*, 498(2), 333-338.

Neuropeptide Y (NPY) administration increases both hypothalamic corticotropin-releasing factor-like immunoreactivity (CRF-ir) and plasma adrenocorticotropin (ACTH). The dependence of these effects on noradrenaline and adrenaline was investigated by selectively depleting these neurotransmitters with 6-hydroxydopamine (6-OHDA) prior to administration of NPY. These data imply that the NPY-induced effects are dependent on normal noradrenergic/adrenergic neurotransmission. Depletion of these neurotransmitters allowed NPY to profoundly stimulate CRF release with no evidence for alteration in synthesis, a result common to alpha 2 stimulation.

Hames, J. (2009). Comprehensive Soldier Fitness. *Soldiers*, 64(8), 4-5.

The article is an investigation into the overall fitness of the Army by assessing aspects of physical, emotional, social, spiritual, and family strength. The goal is to reduce the number of depression and PTSD cases in the Army by making Soldiers not only physically strong, but also emotionally strong.

Henry, J. P. (1992). Biological basis of the stress response. *Integrative Psychological and Behavioral Science*, 27(1), 66-83.

Chronic and emotional arousal are the result of a complex process of interpretations and perceptions of social interactions. When a task or challenge is perceived as easy to handle, the sympathetic system releases norepinephrine. This in turn stimulates the release of testosterone and causes the individual to 'hunger' for success. When a person becomes distressed, they perceive a loss of control of the situation and ACTH and cortisol levels rise. Prolonged periods of ACTH and cortisol release can cause chronic anxiety or depression.

Kilner, P. (2005). The military leader's role in preventing and treating combat-related, perpetration-induced psychological trauma. *Joint Services Conference on Professional Ethics*.

The author discusses the lack of education that Soldiers receive with regard to killing in war. Often times leaders focus on only what happens to Soldiers and not what the actions Soldiers perform. Taking the life of another person is not a subject commonly covered in the army and it has significant implications to as Soldiers inability to adjust once they have done so.

Maguen, S., Vogt, D. S., King, L. A., King, D. W., & Litz, B. T. (2005). Posttraumatic growth among Gulf War I veterans: The predictive role of deployment-related experiences and background characteristics. *Journal of Loss and Trauma, 10*(4), 373-389.

Military status and perceived threat proved to be significant indicators of appreciation of life based off the survey mailed to Gulf War I veterans. Social support best predicted the ability of a soldier to relate to others, their personal strength and their posttraumatic growth from their combat experience. They found that post-deployment support was the only significant predictor of PTG with a $p < .05$. Soldiers who had the highest perceived threat while deployed strongly correlated with a greater appreciation for life upon returning to the US.

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior, 43*(1), 2-15.

Allostatic overload is the result of the inability to deal with stresses on a daily basis. This is often coined “chronic stress” and it often leads to anxiety, fear, frustration, fatigue, and a general sense of lack of control over the outcome of various situations. There are two types of allostatic overload. Type 1 occurs when the energy demanded by the body exceeds the energy stores of the body and causes the body to enter a state of emergency. Type 2 overload occurs when a social conflict occurs and does not trigger an emergency state of mind. Type 2 can only be counterbalanced through learning or change to an individual’s social structure.

McEwen, B. S. (2006). Protective and damaging effects of stress mediators: Central role of the brain. *Dialogues in Clinical Neuroscience, 8*(4), 367-381.

This article discusses allostatic load and its potential negative effects on the body if not properly managed. The ability to mitigate the effects of a large allostatic load has a direct relation to diet, exercise, substance abuse, and life experiences that develop physiological patterns related to how hormones and neurotransmitters react in the body. The goal of the body is to achieve ‘stability through change’ by continually maintaining certain thresholds of neurotransmitters and hormones in the body.

Miller, L. (1999). Atypical psychological responses to traumatic brain injury: PTSD and beyond. *NeuroRehabilitation, 13*, 79-90.

Discusses the typical PTSD and postconcussion syndrome (PCS) and how they are often misdiagnosed in clinical decision making. Defines PTSD as “a syndrome of emotional and behavioral disturbance following exposure to a traumatic stressor that injures or threatens self or others, and that involves the experience of intense fear, helplessness, or horror.” Additionally it lists typical symptoms of PTSD to anxiety, continuous arousal, and withdrawal from social situations.

Morgan, C. A., Wang, S., Southwick, S. M., Rasmousson, A., Hazlett, G., Hauger, R. L., & Charney, D. S. (2000). Plasma neuropeptide-y in humans exposed to military survival training. *Biological Psychiatry*, 47(15), 902-909.

Neuropeptide Y is especially concentrated in the amygdala and clinical studies show it to be an effective buffer against stress. The authors measured plasma NPY levels of Soldiers at the beginning and end of the US Army survival school, as well as during the POW phase and immediately after an interrogation in the POW phase. They found that Special Forces Soldiers were able to more readily return to baseline NPY levels after exposure to extreme stress. Non-SF Soldiers endured a significantly lower baseline NPY level 24 hours after the completion of the survival school.

Morgan, C.A. et al. (2002). Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: replication and extension of previous report. *Biological Psychiatry*, 52(2), 136-142.

These data replicate our previous studies demonstrating that acute stress elicits NPY release and that this release is positively associated with cortisol and NE release. These data also replicate our previous finding that greater levels of NPY release are associated with less psychological distress suggesting that NPY confers anxiolytic activity.

Ong, A. D., Bergman, S. C., Bisconti, T. L., & Wallace, K. A. (2006). Psychological resilience, positive emotions, and successful adaptation to stress in later life. *Journal of Personality and Social Psychology*, 91(4), 730-749.

The authors evaluated resilience to stress at three different levels from daily stressors to bereaved widows. They found that positive emotions experienced daily serve as a mediator towards stress recovery. They particularly address the effects of mediating daily stressors in later adulthood.

Painsipp, E. et al. (2009). Evidence from knockout mice that neuropeptide-Y Y2 and Y4 receptor signaling prevents long-term depression-like behaviour caused by immune challenge. *The Journal of Psychopharmacology*, (Epub ahead of print).

Neuropeptide Y participates in the acute behavioural responses to immune challenge, since Y2 receptor knockout (Y2^{-/-}) mice are particularly sensitive to the short-term anxiogenic-like effect of bacterial lipopolysaccharide. The present exploratory study addressed the involvement of Y2 and Y4 receptors in the long-term behavioural responses to immune challenge. These findings suggest that neuropeptide Y acting via Y2 and Y4 receptors prevents the development of long-term anxiety- and depression-like behaviour caused by acute immune challenge.

Pietrzak, R. H., Johnson, D. C., Goldstein, M. B., Malley, J. C., & Southwick, S. M. (2009). Psychological resilience and post-deployment social support protect against traumatic stress and depressive symptoms in Soldiers returning from Operations Enduring Freedom and Iraqi Freedom. *Depression & Anxiety*, 745-751.

This study compares 272 Operation Iraqi Freedom and Operation Enduring Freedom National Guard veterans from Connecticut on resilience and social support via survey. They found that resilient people were comparable to civilian primary-care outpatients in resilience. Additionally they found that PTSD also correlated negatively with social support levels, suggesting that social support is a key component of resilience. Positive factors that promote resilience are social support, hardiness, perceived support, and perception of worth and helpfulness. These help reduce the risk of depression and negative reactions to traumatic stress.

Roemer, L., Litz, B. T., Orsillo, S. M., Ehlich, P. J., & Friedman, M. J. (1998). Increases in retrospective accounts of warzone exposure over time: The role of PTSD symptom severity. *Journal of Traumatic Stress*, 11(3), 597-605.

Investigates the peace-keeping mission in Somalia on a group of 460 soldiers. Suggests the possibility that severity of symptoms leads to increased reports of stressor frequency. Extreme stress and trauma situations could potentially be used to predict the correlation to anxiety and the “exaggeration” of combat exposure as time progresses. Somalia veterans took a questionnaire within one year of returning to the United States and were then interviewed over the phone 21 months later.

Sah, R. et al. (2009). Low cerebrospinal fluid neuropeptide Y concentrations in posttraumatic stress disorder. *Biological Psychiatry*, 66(7), 705-707.

As compared with the non-PTSD comparison subjects, PTSD patients had significantly lower concentrations of CSF neuropeptide Y (mean CSF NPY was 360.0 ± 17.7 pg/mL in control subjects but only 233.6 ± 28.7 pg/mL in PTSD patients [$p = .0008$]). Adjustments for age and body mass index (BMI) still revealed a highly significant reduction in CSF NPY in the PTSD group ($p = .003$).

Sajdyk, T. et al. (2008). Neuropeptide Y in the amygdala induces long-term resilience to stress-induced reductions in social responses but not hypothalamic–adrenal–pituitary axis activity or hyperthermia. *The Journal of Neuroscience*, 28(4), 893-903.

Rats receiving an iterated injection of NPY into the basolateral nucleus of the amygdala (BLA) show stress-resilient behavior when responding to short-term challenges concerning social interactions. However, NPY does not directly affect HPA axis activity or stress-induced increases in body temperature, meaning the HPA axis reacts the same towards uncontrollable stress. This could potentially be the result of other mechanisms that promote neuronal plasticity towards a resilience to stress.

Selye, H. (1998). A syndrome produced by diverse noxious agents. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 10(2), 230-231.

The author exposed rats to a number of different severe stress scenarios to include exposure to cold, surgical injury and excessive muscular exercise. He found that there is a general three step process in reaction to the initial injury called alarm, resistance and exhaustion. The first stage consists primarily of the shrinking of organs glands and tissue as well as loss of muscle tone. In the second stage, adrenals are greatly enlarged and the animal is put into a high state of "fight." In the last stage the animal is completely exhausted and can no longer physiologically fight without treatment or an end to the stressor.

Tugade, M. M., Fredrickson, B. L., & Barrett, L. F. (2004). Psychological resilience and positive emotional granularity: Examining the benefits of positive emotions on coping and health. *Journal of Personality*, 72(6), 1163-1190.

There are a number of health benefits that potentially result from positive emotion elicitation. Psychological resilience and positive emotion granularity may have a significant link to one another that foster better emotional and physiological well-being.

Walker, M. et al. (2008). The novel neuropeptide Y Y5 receptor antagonist Lu AA33810 exerts anxiolytic-like and antidepressant-like effects in rat models of stress-sensitivity. *The Journal of Pharmacology and Experimental Therapeutics*, 328(3), 900-911.

Neuropeptide Y (NPY) regulates physiological processes via receptor subtypes (Y1, Y2, Y4, Y5, y6). The Y5 receptor is well-known for its role in appetite. Based on expression in the limbic system, they hypothesized that the Y5 receptor might also modulate stress-sensitivity. The authors identified a novel Y5 receptor-selective antagonist, Lu AA33810, that bound to cloned rat Y5 receptors ($K_i = 1.5$ nM) and antagonized NPY-evoked cAMP and calcium mobilization *in vitro*. Lu AA33810 (3-30 mg/kg, p.o.) blocked feeding elicited by i.c.v. injection of Y5 receptor-selective agonist cPP(1-7), NPY(19-23), Ala31, Aib32, Gln34] in Sprague-Dawley rats.

White, B.D. et al. (1994). Type II corticosteroid receptor stimulation increases NPY gene expression in basomedial hypothalamus of rats. *The American Journal of Physiology*, 266(5), 1523-1529.

Evidence suggests that glucocorticoids may increase neuropeptide Y (NPY) activity and gene expression. In the present study, the authors sought to determine the corticosteroid receptor subtype through which glucocorticoids increase NPY gene expression in the basomedial hypothalamus. The present results may have relevance to the increased gene expression of NPY observed in the basomedial hypothalamus of obese Zucker rats and in food-deprived animals.

Wood, D. P., Murphy, J., Center, K., Mclay, R., Reeves, D., Pyne, J., & Shilling, R. (2007). Combat-related post-traumatic stress disorder: A case report using virtual reality exposure therapy with physiological monitoring. *CyberPsychology & Behavior*, 10(2), 309-315.

Compares virtual reality graded exposure therapy (VRGET) to cognitive behavioral group therapy of active duty Naval corpsmen. They found that ten, ninety minute sessions of virtual reality combat exposure decreased the symptoms of PTSD 15-67% over a six month period. The experiment was performed on recently returned OIF/OEF veterans. VRE helps a patient become emotionally engaged in a virtual combat scenario. With time the corpsmen learned that they could manage extremely stressful situations and reported being better able to focus attention and develop meditation techniques to relieve stress. Initially the corpsmen reported having to “decompress” for 1-2 hours after each of the beginning sessions due to the VRE being so emotionally engaging.

Yehuda, R. (2002). Current status of cortisol findings in post-traumatic stress disorder. *Psychiatric Clinics of North America*, 25(2), 341-368.

The HPA axis is one of the primary responders to extreme stress. The hypothalamus secretes CRF, which stimulates the pituitary gland to release ACTH, which then stimulates the adrenal gland to release cortisol. Over activation of the HPA axis has severe effects on both cognitive and physiological processes. Overstimulation is often the result of prolonged and untreated traumatic stress that places the body in a constant state of alertness and anxiety.

Yehuda, R. et al. (2006). Plasma neuropeptide Y concentrations in combat exposed veterans: relationship to trauma exposure, recovery from PTSD, and coping. *Biological Psychiatry*, 59(7), 660-663.

To further investigate this possibility, plasma NPY was measured in 11 non-exposed veterans, 11 combat-exposed veterans without posttraumatic stress disorder (PTSD), and 12 veterans with current PTSD. A significant group difference in plasma NPY ($F(2,31) = 5.16, p = .012$) was observed, reflecting higher NPY levels in exposed veterans without PTSD than in non-exposed but comparable levels in veterans with current PTSD. Among those without current PTSD, veterans with past PTSD had higher NPY levels than those without past PTSD ($t(9) = 2.71, p = .024$). After controlling for all other variables, NPY levels were significantly predicted by extent of symptom improvement and lower combat exposure and significant at a trend level with positive coping.