



# PTSD *Research Quarterly*

ADVANCING SCIENCE AND PROMOTING UNDERSTANDING OF TRAUMATIC STRESS

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## Biomarkers for Treatment and Diagnosis

### Introduction

We appear to have reached a watershed in the development of biologically based interventions for the prevention and treatment of PTSD. Over the past 25 years, great strides have been made in the characterization of biological characteristics of PTSD (Pitman et al., 2012), but there remain few biologically oriented treatments for PTSD with proven efficacy, either as stand-alone pharmacotherapies or as augmentation for otherwise generally effective exposure-based cognitive therapies such as Prolonged Exposure (PE) or Cognitive Processing Therapy (CPT). Pharmacological agents tested in PTSD have typically shown large effect sizes in at least some small scale preliminary studies, but considerably smaller effects when tested against placebo in large multisite trials. Even the two United States (US) Food and Drug Administration (FDA)-approved medications for PTSD (the serotonin-selective reuptake inhibitors, sertraline and paroxetine), showed only moderate effect sizes in four large FDA registrational trials conducted in general PTSD populations (Friedman and Davidson, 2014). Although there may be many reasons for the limited success in this area of PTSD treatment development, a primary reason may be the failure to address individual variability in the complex interacting biological processes that converge on the otherwise relatively uniform PTSD phenotype or that define PTSD endophenotypes or particular PTSD-related medical, psychiatric, and substance abuse comorbidity patterns. However, rapidly evolving molecular, neuroimaging, psychophysiology, and data analytic strategies embedded in new multimodal study designs may afford new opportunities to capitalize on this earned insight—in the service of developing individually based precision biotherapies for PTSD and PTSD-related

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comorbid conditions. The following brief bibliography has therefore been assembled to guide clinical and basic scientists through the accumulated translational knowledge base of biological factors related to PTSD risk and constituting potential PTSD treatment targets or outcome variables. The list has been limited in accordance with space and is by no means exhaustive; rather, it is intended to highlight the discovery of critical biological factors and emergence of concepts that have advanced PTSD investigations to the current vantage point.

### Neuroendocrine Systems

#### *Monoamine and Peptide Transmitters*

A pharmacological challenge study by Southwick et al. (1993) was among the most influential early studies to define the molecular underpinnings of autonomic nervous system hyperreactivity associated with PTSD (Pitman et al., 1987). In this study, administration of the noradrenergic alpha-2 receptor antagonist, yohimbine, induced marked noradrenergic system hyperreactivity in association with heightened cardiovascular and PTSD symptom responses in male Vietnam Veterans. Excessive PTSD-related noradrenergic system reactivity has been replicated in both men and women and constitutes the most consistent biological abnormality in PTSD to date. However, subsequent work by Southwick et al. (1997) demonstrated that PTSD symptoms were uniquely exacerbated by yohimbine-induced noradrenergic system activation in only one-third of the cohort of Vietnam Veterans, whereas a serotonin type-2A (5HT<sub>2A</sub>) receptor agonist (meta-chlorophenylpiperazine or mCPP) activated PTSD symptoms in another third, and both the noradrenergic and serotonergic system probes

*Continued on page 2*



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activated symptoms in yet another third. This study thus clearly demonstrated subpopulation variability in the neurobiological systems that mediate PTSD symptoms, and supported the idea that treatments for PTSD may need to be individually targeted. Consistent with these findings, Raskind et al. (2007), demonstrated salutary effects of a selective noradrenergic alpha-1 receptor antagonist on sleep quality and nightmares in 71% of a cohort of Veterans with PTSD. Current work is exploring the utility of alpha-1 blockers for treatment of daytime PTSD symptoms. Future work will hopefully make use of already identified genetic, epigenetic, and clinical biomarkers of noradrenergic hyperreactivity to aid in pre-treatment matching between such interventions and likely responders.

Marked decreases in resting plasma neuropeptide Y (NPY) levels and blunted NPY responses to yohimbine were also found in the aforementioned cohort of Vietnam Veterans with yohimbine-induced noradrenergic hyperreactivity (Rasmusson et al., 2000). NPY levels correlated positively with bodyweight and inversely with noradrenergic, cardiovascular, and PTSD symptom responses to yohimbine. As NPY is colocalized with norepinephrine in sympathetic neurons, and with multiple other neurotransmitters in systems distributed throughout the brain and periphery, this study introduced the possibility that abnormalities in one broad-impact neurobiological factor may result in multiple comorbid stress-related medical and psychiatric conditions (e.g., Rasmusson et al., 2010; Scioli et al., 2014). Subsequent work by Sah et al. (2009) confirmed decreased cerebrospinal fluid (CSF) NPY levels in men with PTSD. In contrast, work by Morgan et al. (2000) has shown a positive relationship between peak plasma NPY levels and military performance among active duty personnel participating in intensely stressful survival school exercises, a negative relationship between NPY and dissociation during peak stress, and a negative relationship between dissociation and performance—thus demonstrating NPY's reciprocal role in stress resilience. Work by Yehuda et al. (2006 and 2014) has further defined NPY as a predictor of PTSD recovery. The influence on NPY synthesis of sex steroids, genetic factors (Karvonen et al., 2001; Zhou et al., 2008; Zhang et al., 2012), and epigenetic processes now suggests that dysregulation of this system may arise from a variety of individually-variable processes—which in turn may serve as individualized targets for interventions aimed at reducing the risk for PTSD and PTSD-related medical comorbidities.

Corticotropin-releasing factor (CRF) is another peptide dysregulated in PTSD. Bremner et al. (1997) demonstrated increased CRF levels in the CSF of male Veterans with PTSD, a finding replicated in other male PTSD cohorts (e.g., Baker et al., 1999), but not yet studied in women. CRF in this compartment is thought to reflect extrahypothalamic CRF, which mediates increases in fear and anxiety-related behavior, in part by antagonizing effects of NPY. Subsequent attempts to pharmacologically target the CRF system in the treatment of PTSD have failed due to liver toxicity, but efforts in this area of treatment development continue.

Most recently, animal work has shown a role for endocannabinoids in stress adaptation and fear extinction, leading Neumeister et al. (2013) to conduct a positron emission tomography (PET) investigation

of cannabinoid type 1 (CB1) receptors in PTSD. Elevated brain cannabinoid CB1 receptor availability was found in the PTSD group, particularly in women. The PTSD group also had lower plasma levels of cortisol and the endocannabinoid, anandamide. A subsequent study by Hill et al. (2013) has demonstrated low levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) in a small cohort of individuals with PTSD exposed to the 9/11 World Trade Center attack. Therefore, although basic research suggests that direct cannabinoid receptor agonists are unlikely to be useful in reducing PTSD, these studies suggest that indirect strategies to upregulate endocannabinoid system function may have value.

### *Steroids*

Study of the glucocorticoid system in PTSD has yielded variable results, which continue to be reinterpreted as scientific experience with the complex features of this system accumulates. Yehuda et al. (1995) conducted the first study to demonstrate alterations in glucocorticoid receptor number and function in association with trauma exposure and/or PTSD, and introduced the concept of glucocorticoid receptor supersensitivity. Work over time, however, has demonstrated variability in tests of glucocorticoid feedback among PTSD populations, as well as variability in resting cortisol levels and responses to provocation. To more definitively define the function of the glucocorticoid system in PTSD, Shalev et al. (2008) undertook a large prospective study of individuals presenting to an acute care setting in the aftermath of acute trauma—and demonstrated no predictive relationship between cortisol levels and PTSD risk, although a relationship was found between high adrenocorticotropin (ACTH) levels and PTSD risk in women. However, using a machine learning approach in the same cohort, Galatzer-Levy et al. (2014) most recently demonstrated a link between low cortisol levels and PTSD risk, but only among study participants with a history of childhood trauma. In support of the relevance of early childhood trauma to adult endocrine profiles, work by Klengel et al. (2013) has elegantly demonstrated the presence of a childhood developmental window for epigenetic dysregulation of an FKBP5 gene which increases the risk for stress-related PTSD—leading to deficient function of the glucocorticoid receptor. Individuals so affected have increased and prolonged cortisol responses to stress and increased risk for peritraumatic stress reactions, as well as increased risk for PTSD and depression as adults. This phenomenon thus may account for studies finding increased ACTH and/or cortisol levels in cohorts of women with PTSD, comorbid depression, and high rates of childhood trauma. An increase in expression of FKBP5 during cognitive behavioral treatment has been shown to predict treatment efficacy.

Most recently, the variability in glucocorticoid system function in PTSD has been embraced as a predictor of treatment outcome. Yehuda et al. (2014) measured selected stress system biomarkers before and after evidence-based PE therapy and a Minimal Attention (MA) condition in male and female Veterans with PTSD. Higher bedtime salivary cortisol levels, possession of BCL1 glucocorticoid receptor genotypes associated with increased glucocorticoid receptor sensitivity, and higher plasma NPY levels predicted PTSD remission across both conditions. Higher NPY levels at baseline were also associated with better global mental health after treatment. In addition, glucocorticoid receptor sensitivity decreased, while 24-hour cortisol levels increased

across treatment in responders. In non-responders, 24-hour urinary cortisol levels decreased, while glucocorticoid receptor sensitivity increased across treatment. This is one of the first studies to simultaneously investigate the relationship between more than one system of biomarkers and treatment outcome, while characterizing functional interactions between biomarkers within systems. It will be important in future studies to consider many more systems and their functional interactions to more fully understand the mechanisms that influence PTSD risk and recovery at the individual level.

Dysregulation of other steroid systems also plays a role in PTSD risk and severity. Rasmusson et al. (2006) first demonstrated a deficit in progesterone metabolites that potently and positively modulate the inhibitory effects of gamma-amino-butyric acid (GABA) at GABAA receptors in women with PTSD. Low CSF levels of allopregnanolone and its equipotent stereoisomer, pregnanolone (apparently related to an enzymatic block in allopregnanolone synthesis) correlated strongly with the severity of PTSD re-experiencing and depression symptoms. Animal research has shown that SSRIs at low doses reduce PTSD-like symptoms by increasing levels of allopregnanolone, suggesting that allopregnanolone synthesis deficits in PTSD patients may contribute to SSRI treatment resistance. Development of pharmacotherapies targeting such deficits are thus of interest.

Alterations in dehydroepiandrosterone (DHEA), which facilitates excitatory n-methyl-D-aspartate (NMDA) receptor function and antagonizes GABAA receptors, also have been found in PTSD. Increased DHEA/cortisol levels at peak stress or in reaction to maximum adrenal activation, or increased levels of DHEAS (the more potent sulfated metabolite of DHEA stored in tissues for use during stress) have been found to predict military stress resilience in men (Morgan et al., 2003), lower PTSD symptom burden and depression in women (Rasmusson et al., 2004), and greater improvement in PTSD symptoms over time (Yehuda et al., 2006). However, a lower resting ratio of DHEA to cortisol has been associated both with childhood trauma (Yehuda et al., 2006) and with lower PTSD symptom severity after treatment (Yehuda et al., 2014). This suggests the importance of assessing childhood trauma, as well as distinguishing between resting and stress reactive ratios of DHEA to cortisol when using this metric as a biopredictor. As observed by Rasmusson et al. (2004), the ratio of DHEA to cortisol increased in response to maximum adrenal gland activation among trauma-exposed individual with and without PTSD, but decreased among non-traumatized individuals. Thus a lower resting DHEA to cortisol ratio may reflect less sensitivity to mild environmental stress among individuals with less severe PTSD. A higher DHEA/allopregnanolone ratio in CSF has been linked to greater re-experiencing and negative mood symptoms in women with PTSD (Rasmusson et al., 2006), suggesting that the balance of excitatory to inhibitory neurotransmission may be critical to PTSD symptom pathogenesis.

## Genetics

Molecular genomics studies are multiplying and promise to contribute significantly to our understanding of mechanisms underlying PTSD risk. For example, epigenetic studies investigate functionally relevant changes to deoxyribonucleic acid (DNA) that do not involve a change in the nucleotide sequence and that may

result from environmental influences. Epigenetic mechanisms include methylation of individual nucleotides and histone modifications (e.g., acetylation) that alter gene expression without altering the underlying DNA sequence. Uddin et al. (2010) conducted the first epigenetics study demonstrating differences in DNA methylation profiles between PTSD affected and unaffected groups. Using samples from the Detroit Neighborhood Health Study, the investigators found that PTSD was associated with altered immunological function as indicated by decreased methylation of immune system genes in association with increased titers of antibodies to an infectious agent with high community prevalence. This work is consistent with a growing number of studies showing alterations in inflammatory factors in PTSD (e.g. Gill et al., 2008), suggesting the potential for future work in this area to help explain the high comorbidity between PTSD and multiple negative physical health sequelae of traumatic stress.

Ressler et al. (2011) conducted the first study demonstrating sex differences in a genetic risk factor for PTSD. A single nucleotide polymorphism (SNP) in a putative estrogen response element within the promoter for a gene (ADCYAP1R1) encoding the pituitary adenylate cyclase-activating polypeptide (PACAP) receptor (PAC1) predicted PTSD diagnosis and symptoms in females only. This finding may partially explain the higher prevalence of PTSD among females. Furthermore, considering the link between testosterone conversion to estrogen and aggression in males, it may be important to consider the role of such an estrogen dependent gene in PTSD even in male subpopulations. A subsequent study (Gillespie et al., 2013) demonstrated increased risk for PTSD in men with an apparent loss-of-function polymorphism in the gene coding for 5 $\alpha$ -reductase-2, which converts testosterone to its more potent metabolite, 5 $\alpha$ -dihydrotestosterone (5 $\alpha$ -DHT), which is, in turn, metabolized to an inhibitory GABAergic neuroactive steroid (3 $\alpha$ -diol). 5 $\alpha$ -DHT may also serve to upregulate genes for enzymes that produce other resilience-related factors such as NPY or allopregnanolone. Yehuda et al. (2009) has shown that a reduction in the activity of 5 $\alpha$ -reductase predicts poor outcome in response to a brief series of prolonged exposure therapy sessions.

Logue et al. (2013) conducted the first genome-wide association study (GWAS) in PTSD and established the retinoid-related orphan receptor alpha (RORA) gene as a PTSD risk locus. RORA is a nuclear hormone receptor involved in the protection of neurons and glia from oxidative stress, and RORA dysfunction is associated with reductions in grey and white matter integrity. RORA is also involved in brain development and regulation of circadian rhythms and steroid hormones. In a GWAS by Wolf et al. (2014), the ADCY8 and DPP6 genes were implicated in the new DSM-5 dissociative subtype of PTSD. ADCY8 is integral to long-term potentiation and synaptic plasticity, while DPP6 is critical for integration of synaptic inputs and neuronal excitation. Thus both are critical to sensory integration and cognitive processing of experience.

## Psychophysiology Studies

Many studies have demonstrated increased reactivity to trauma-related cues and unconditioned noxious stimuli in PTSD (e.g., Pitman et al., 1987; Orr et al., 2003). They have also

demonstrated a variety of PTSD-related abnormalities in fear conditioning paradigms—including diminished extinction retention (Milad et al., 2009) and failure to inhibit learned fear in the context of learned safety signals (e.g., Jovanovic et al., 2013). Objective and subjective studies of PTSD-related sleep disturbances have also revealed a variety of sleep architecture abnormalities (Woodward et al., 2000; Richards et al., 2013; Kobayashi and Mellman, 2012). Objective and subjective sleep deficits in PTSD have been mapped onto abnormal nighttime peripheral noradrenergic indices and brain GABA and glutamate levels, respectively (Mellman et al., 1995 and Meyerhoff et al., 2014).

## Brain Imaging

Bremner et al (1995) provided the first evidence of decreased hippocampal volume in PTSD, a brain region related to memory and fear extinction. Several studies, but not all, have replicated this finding in PTSD, depression, and various other psychiatric disorders. Gray matter reductions in PTSD have also been demonstrated in other brain regions (e.g. anterior cingulate). These findings are consistent with a hypothetical model in which stress dysregulates hypothalamic-pituitary-adrenal (HPA) axis and glial function, leading to increased glutamate excitotoxicity, and subsequent gray matter reduction. Supporting this model, pilot studies have shown normalization of hippocampal structure and function following treatment (Levy-Gigi et al., 2013; reviewed by Thomaes et al. 2014). A subsequent elegant twin study by Gilbertson et al. (2002) has provided strong evidence for small hippocampus size as a predisposing factor for PTSD, rather than a consequence. More recent work has presented a more complex picture wherein altered brain structures constitute both vulnerabilities to and outcomes of posttraumatic stress (Sekiguchi et al. 2013).

Reduced prefrontal cortex, but increased amygdala, activation in response to emotional processing (see Phan et al., 2002), has been repeatedly—but not consistently—demonstrated in PTSD. Etkin et al. (2007) therefore undertook a meta-analysis and confirmed these abnormalities. The specificity of the prefrontal impairment to PTSD was also demonstrated, supporting a PTSD model of reduced top-down control combined with increased bottom-up emotional sensitization. In contrast, in the dissociative subtype of PTSD, Lanius et al. (2012) found an increase in limbic inhibition by the midline prefrontal cortex.

Shin et al. (2011) used the Vietnam Twin Registry to confirm previous work suggesting that enhanced resting metabolic activity in the dorsal anterior and medial cingulate cortices (dACC/MCC) constitutes a familial risk factor, rather than state marker for PTSD. In this study, Shin et al. demonstrated that combat-exposed Veterans with PTSD and their unexposed co-twins had significantly greater activation in the dorsal anterior cingulate and a larger response time difference scores on the Multi-Source Interference Task, as compared to combat Veterans without PTSD and their co-twins.

Finally, a proof-of-concept study by Bryant et al. (2008) demonstrated the possible utility of imaging biomarkers in predicting treatment response. Other PTSD studies have shown that gray matter abnormalities predict poor response to cognitive behavior therapy (CBT) and eye movement desensitization and

reprocessing (EMDR) therapy. In depression, brain structural deficits have been related to poor response to serotonergic drugs, but enhanced response to glutamatergic antidepressants, suggesting the presence of a subpopulation of patients with possible glutamate-based abnormalities leading to structural deficits and treatment resistance to serotonergic drugs (Abdallah et al. 2014).

## Summary

A survey of the extant literature supports roles for a variety of interacting stress responsive factors in the pathogenesis of PTSD as well as the medical and other psychiatric features with which PTSD is commonly comorbid. Some factors such as adoption of nicotine or alcohol abuse on a casual basis or with the intention of self-treating stress-related symptoms may alter neuroendocrine profiles in directions that mimic the effects of naturally acquired PTSD risk factors (e.g. Cagetti et al., 2004; Koenen et al., 2005). Understanding and addressing the epigenetic or more direct regulatory effects of such environmental risk factors thus will be as important as revealing interactive genetic PTSD risk factors—so that individualized interventions can be appropriately targeted. Indeed, understanding bottom up individual points of malfunction in particular stress systems will be critical to the differential diagnosis and targeting of effective individualized treatments. For example, parsing out how epigenetic changes in the function of healthy genes mimic the effects of less healthy gene polymorphisms will strengthen our capacity to identify key pathogenetic pathways to PTSD as well as enable the targeted use of promising epigenetic treatments ranging from the exercise of particular brain circuits to exercise itself to the employment of epigenetics based pharmaceutical strategies. In support of these efforts, the emergence of fully translational study designs, and use of cutting edge data analytic strategies that embrace the real complexities of biological systems and allow for both direct testing of hypotheses as well as discovery within a common large dataset hold great promise. The related redesign of treatment trials to identify and enroll individuals possessing biological deficits to which particular treatments are matched or to enable identification of signals from true responder subpopulations can then speed development of more effective interventions for PTSD prevention and treatment.

## FEATURED ARTICLES

Bremner, J.D., Randall, P., Scott, T.M., Bronen, R.A., Seibyl, J.P., Southwick, S.M., et al. (1995). **MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder.** *American Journal of Psychiatry*, 152, 973-981. *Objective:* Studies in nonhuman primates suggest that high levels of cortisol associated with stress have neurotoxic effects on the hippocampus, a brain structure involved in memory. The authors previously showed that patients with combat-related PTSD had deficits in short-term memory. The purpose of this study was to compare the hippocampal volume of patients with PTSD to that of subjects without psychiatric disorder. *Method:* Magnetic resonance imaging was used to measure the volume of the hippocampus in 26 Vietnam combat Veterans with PTSD and 22 comparison subjects selected to be

similar to the patients in age, sex, race, years of education, socioeconomic status, body size, and years of alcohol abuse. *Results:* The PTSD patients had a statistically significant 8% smaller right hippocampal volume relative to that of the comparison subjects, but there was no difference in the volume of other brain regions (caudate and temporal lobe). Deficits in short-term verbal memory as measured with the Wechsler Memory Scale were associated with smaller right hippocampal volume in the PTSD patients only. *Conclusions:* These findings are consistent with a smaller right hippocampal volume in PTSD that is associated with functional deficits in verbal memory.

Bremner, J.D., Licinio, J., Darnell, A., Krystal, J.H., Owens, M.J., Southwick, S.M., et al. (1997). **Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder.** *The American Journal of Psychiatry*, 154, 624–629.

*Objective:* Corticotropin-releasing factor (CRF) and somatostatin both play important roles in mediating responses to acute and chronic stress. The purpose of this study was to measure CSF concentrations of CRF and somatostatin in patients with chronic combat-related PTSD and comparison subjects. *Method:* Lumbar punctures for collection of CSF were performed in Vietnam combat Veterans with PTSD ( $N = 11$ ) and comparison subjects ( $N = 17$ ). CSF concentrations of CRF and somatostatin were compared between the two groups. *Results:* CSF concentrations of CRF were higher in the PTSD patients than in the comparison subjects (mean = 29.0 picograms per milliliter [pg/ml], SD = 7.8, versus mean = 21.9 pg/ml, SD = 6.0). This group difference remained significant after covariance for age. CSF somatostatin concentrations in PTSD patients were higher than those of the comparison subjects (mean = 19.9 pg/ml, SD = 5.4, versus mean = 13.7 pg/ml, SD = 8.0). However, co-varying for age reduced the level of significance. *Conclusions:* 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.

Bryant, R.A., Felmingham, K., Kemp, A., Das, P., Hughes, G., Peduto, A., et al. (2008). **Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder.** *Psychological Medicine*, 38, 555–561. doi:10.1017/S0033291707002231

*Background:* Although CBT is the treatment of choice for PTSD, approximately half of patients do not respond to CBT. No studies have investigated the capacity for neural responses during fear processing to predict treatment response in PTSD. *Method:* Functional magnetic resonance imaging (fMRI) responses of the brain were examined in individuals with PTSD ( $n=14$ ). fMRI was examined in response to fearful and neutral facial expressions presented rapidly in a backwards masking paradigm adapted for a 1.5 T scanner. Patients then received eight sessions of CBT that comprised education, imaginal and *in vivo* exposure, and cognitive therapy. Treatment response was assessed 6 months after therapy completion. *Results:* Seven patients were treatment responders (defined as a reduction of 50% of pretreatment scores) and seven were non-responders. Poor improvement after treatment was associated with greater

bilateral amygdala and ventral anterior cingulate activation in response to masked fearful faces. *Conclusions:* Excessive fear responses in response to fear-eliciting stimuli may be a key factor in limiting responses to CBT for PTSD. This excessive amygdala response to fear may reflect difficulty in managing anxiety reactions elicited during CBT, and this factor may limit optimal response to therapy.

Etkin, A., & Wager, T.D. (2007). **Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia.** *American Journal of Psychiatry*, 164, 1476–1488. doi:10.1176/appi.ajp.2007.07030504 *Objective:* The study of human anxiety disorders has benefited greatly from functional neuroimaging approaches. Individual studies, however, vary greatly in their findings. The authors searched for common and disorder-specific functional neurobiological deficits in several anxiety disorders. The authors also compared these deficits to the neural systems engaged during anticipatory anxiety in healthy subjects. *Method:* Functional magnetic resonance imaging and positron emission tomography studies of PTSD, social anxiety disorder, specific phobia, and fear conditioning in healthy individuals were compared by quantitative meta-analysis. Included studies compared negative emotional processing to baseline, neutral, or positive emotion conditions. *Results:* Patients with any of the three disorders consistently showed greater activity than matched comparison subjects in the amygdala and insula, structures linked to negative emotional responses. A similar pattern was observed during fear conditioning in healthy subjects. Hyperactivation in the amygdala and insula were, of interest, more frequently observed in social anxiety disorder and specific phobia than in PTSD. By contrast, only patients with PTSD showed hypoactivation in the dorsal and rostral anterior cingulate cortices and the ventromedial prefrontal cortex—structures linked to the experience and regulation of emotion. *Conclusions:* This meta-analysis allowed us to synthesize often disparate findings from individual studies and thereby provide neuroimaging evidence for common brain mechanisms in anxiety disorders and normal fear. Effects unique to PTSD furthermore suggested a mechanism for the emotional dysregulation symptoms in PTSD that extend beyond an exaggerated fear response. Therefore, these findings help refine our understanding of anxiety disorders and their interrelationships.

Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P., et al. (2002). **Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma.** *Nature Neuroscience*, 5, 1242–1247. doi:10.1038/nn958 In animals, exposure to severe stress can damage the hippocampus. Recent human studies show smaller hippocampal volume in individuals with the stress-related psychiatric condition PTSD. Does this represent the neurotoxic effect of trauma, or is smaller hippocampal volume a pre-existing condition that renders the brain more vulnerable to the development of pathological stress responses? In monozygotic twins discordant for trauma exposure, we found evidence that smaller hippocampi indeed constitute a risk factor for the development of stress-related psychopathology. Disorder severity in PTSD patients who were exposed to trauma was negatively correlated with the hippocampal

volume of both the patients and the patients' trauma-unexposed identical co-twin. Furthermore, severe PTSD twin pairs—both the trauma-exposed and unexposed members—had significantly smaller hippocampi than non-PTSD pairs.

Gillespie, C.F., Almlı, L.M., Smith, A.K., Bradley, B., Kerley, K., Crain, D.F., et al. (2013). **Sex dependent influence of a functional polymorphism in steroid 5-alpha-reductase type 2 (SRD5A2) on post-traumatic stress symptoms.** *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 162B, 283-292. doi:10.1002/ajmg.b.32147 A non-synonymous, SNP in the gene coding for steroid 5- $\alpha$ -reductase type 2 (*SRD5A2*) is associated with reduced conversion of testosterone to DHT. Because *SRD5A2* participates in the regulation of testosterone and cortisol metabolism, hormones shown to be dysregulated in patients with PTSD, we examined whether the V89L variant (rs523349) influences risk for. Study participants ( $N = 1,443$ ) were traumatized African-American patients of low socioeconomic status with high rates of lifetime trauma exposure recruited from the primary care clinics of a large, urban hospital. PTSD symptoms were measured with the post-traumatic stress symptom scale (PSS). Subjects were genotyped for the V89L variant (rs523349) of *SRD5A2*. We initially found a significant sex-dependent effect of genotype in male but not female subjects on symptoms. Associations with PTSD symptoms were confirmed using a separate internal replication sample with identical methods of data analysis, followed by pooled analysis of the combined samples ( $N = 1,443$ , sex  $\times$  genotype interaction  $p < 0.002$ ; males:  $n = 536$ ,  $p < 0.001$ ). These data support the hypothesis that functional variation within *SRD5A2* influences, in a sex-specific way, the severity of post-traumatic stress symptoms and risk for diagnosis of PTSD.

Jovanovic, T., Sakoman, A.J., Kozaric-Kovacic, D., Mestrovic, A.H., Duncan, E.J., Davis, M., et al. (2013). **Acute stress disorder versus chronic posttraumatic stress disorder: Inhibition of fear as a function of time since trauma.** *Depression & Anxiety*, 30, 217-224. doi:10.1002/da.21991 *Background:* Previous work has shown that inhibition of fear is impaired in PTSD resulting from both civilian and combat trauma. The purpose of the present study was to investigate the inhibition of learned fear in traumatized individuals diagnosed with either acute stress disorder (ASD) or PTSD. This is the first study to use a conditioned inhibition paradigm with traumatized individuals within a month of trauma exposure. We hypothesized that impaired fear inhibition would be evident in PTSD, but not ASD. *Method:* Using established translational, psychophysiological methods including fear-potentiated startle, and skin conductance, we examined fear acquisition, stimulus discrimination, and the transfer of learned safety in a Croatian population with ASD or PTSD. This cross-sectional study included three age-matched groups: healthy non-trauma controls ( $n = 27$ ), a group with chronic PTSD (10 or more years since trauma exposure,  $n = 24$ ), and a group with ASD (30 days or less since trauma exposure,  $n = 27$ ). *Results:* The presence of trauma-related psychopathology, whether acute or chronic, was associated with an impaired ability to transfer learned safety based on fear-potentiated startle measures, while healthy control subjects showed significant fear inhibition in the presence of the safety

cue compared to the danger cue,  $F(1,26) = 12.64$ ,  $p = .001$ . *Conclusions:* These data expand our previously observed findings of PTSD-associated fear inhibition deficits by demonstrating that trauma-related impairments in safety learning are evident within 30 days of trauma exposure.

Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J.C., Pariante, C.M., et al. (2013). **Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions.** *Nature Neuroscience*, 16, 33-41. doi:10.1038/nn.3275 Although the fact that genetic predisposition and environmental exposures interact to shape development and function of the human brain and, ultimately, the risk of psychiatric disorders has drawn wide interest, the corresponding molecular mechanisms have not yet been elucidated. We found that a functional polymorphism altering chromatin interaction between the transcription start site and long-range enhancers in the FK506 binding protein 5 (*FKBP5*) gene, an important regulator of the stress hormone system, increased the risk of developing stress-related psychiatric disorders in adulthood by allele-specific, childhood trauma-dependent DNA demethylation in functional glucocorticoid response elements of *FKBP5*. This demethylation was linked to increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global effect on the function of immune cells and brain areas associated with stress regulation. This identification of molecular mechanisms of genotype-directed long-term environmental reactivity will be useful for designing more effective treatment strategies for stress-related disorders.

Koenen, K.C., Hitsman, B., Lyons, M.J., Niaura, R., McCaffery, J., Goldberg, J., et al. (2005). **A twin registry study of the relationship between posttraumatic stress disorder and nicotine dependence in men.** *Archives of General Psychiatry*, 62, 1258-1265. doi:10.1001/archpsyc.62.11 *Context:* Recent studies indicate a strong association between PTSD and nicotine dependence (ND). However, the explanation for the association remains unclear. *Objective:* To test competing explanations for the association between PTSD and ND. *Design, Setting, and Participants:* Analysis of data on 6744 members of the Vietnam Era Twin Registry, a national registry of all male-male twin pairs who served in the military during the Vietnam era interviewed in 1991-1992. *Main Outcome Measures:* Risk of PTSD and ND using the Diagnostic Interview Schedule for the *DSM-III-R*. *Results:* The prevalence of ND was elevated among trauma-exposed individuals (52.0%) and those with PTSD (71.7%) compared with unexposed individuals (40.5%). This association was significant for ND and for trauma without PTSD (odds ratio, 1.31; 95% confidence interval [CI], 1.18-1.45) and for PTSD (odds ratio, 2.34; 95% CI, 1.92-2.84) and was not entirely explained by shared risk factors. Shared genetic effects explained 63% of the PTSD-ND association; the remaining covariance was explained by individual-specific environmental effects. Using survival analysis with time-dependent covariates, ND was associated with a substantially increased risk of PTSD among trauma-exposed men (hazard ratio, 1.98; 95% CI, 1.61-2.42). Trauma (hazard ratio, 1.49; 95% CI, 1.35-1.64) and PTSD (hazard ratio, 1.36; 95% CI, 1.14-1.61) were less strongly

but significantly associated with increased risk of ND onset after controlling for shared risk factors. *Conclusions:* Most of the PTSD-ND association is explained by shared genetic effects. However, there is a substantial, robust PTSD-ND association not explained by shared risk factors. Multiple explanations for the association were supported; however, the strongest association was consistent with preexisting ND increasing the risk of PTSD onset. These data suggest that male Veterans with a history of ND may be at increased risk for PTSD. Further research on the biological mechanisms underlying PTSD-ND comorbidity is needed.

Logue, M.W., Baldwin, C., Guffanti, G., Melista, E., Wolf, E.J., Reardon, A.F., et al. (2013). **A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus.** *Molecular Psychiatry*, 18, 937-942. doi:10.1038/mp.2012.113 We describe the results of the first GWAS of PTSD performed using trauma-exposed white non-Hispanic participants from a cohort of Veterans and their intimate partners (295 cases and 196 controls). Several SNPs yielded evidence of association. One SNP (rs8042149), located in the RORA, reached genome-wide significance. Nominally significant associations were observed for other RORA SNPs in two African-American replication samples—one from the veteran cohort (43 cases and 41 controls) and another independent cohort (100 cases and 421 controls). However, only the associated SNP from the veteran African-American replication sample survived gene-level multiple-testing correction. RORA has been implicated in prior GWAS studies of psychiatric disorders and is known to have an important role in neuroprotection and other behaviorally relevant processes. This study represents an important step toward identifying the genetic underpinnings of PTSD.

Meyerhoff, D.J., Mon, A., Metzler, T., & Neylan, T.C. (2014). **Cortical gamma-aminobutyric acid and glutamate in posttraumatic stress disorder and their relationships to self-reported sleep quality.** *Sleep*, 37, 893-900. doi:10.5665/sleep.3654 *Study Objectives:* To test if PTSD is associated with low brain GABA levels and if reduced GABA is mediated by poor sleep quality. *Design:* Laboratory study using *in vivo* proton magnetic resonance spectroscopy (1H MRS) and behavioral testing. *Setting:* VA Medical Center Research Service, Psychiatry and Radiology. *Patients Or Participants:* Twenty-seven patients with PTSD (PTSD+) and 18 trauma-exposed controls without PTSD (PTSD-), recruited from US Army reservists, Army National Guard, and mental health clinics. *Interventions:* None. *Measurements And Results:* 1H MRS at 4 Tesla yielded spectra from three cortical brain regions. In parieto-occipital and temporal cortices, PTSD+ had lower GABA concentrations than PTSD-. As expected, PTSD+ had higher depressive and anxiety symptom scores and a higher Insomnia Severity Index (ISI) score. Higher ISI correlated with lower GABA and higher glutamate levels in parieto-occipital cortex and tended to correlate with lower GABA in the anterior cingulate. The relationship between parieto-occipital GABA and PTSD diagnosis was fully mediated through insomnia severity. Lower N-acetylaspartate and glutamate concentrations in the anterior cingulate cortex correlated with higher arousal scores, whereas depressive and anxiety symptoms did generally not

influence metabolite concentrations. *Conclusions:* Low brain GABA concentration in PTSD is consistent with most findings in panic and social anxiety disorders. Low GABA associated with poor sleep quality is consistent with the hyperarousal theory of both primary insomnia and PTSD. Our data demonstrate that poor sleep quality mediates low parieto-occipital GABA in PTSD. The findings have implications for PTSD treatment approaches.

Milad, M.R., Pitman, R.K., Ellis, C.B., Gold, A.L., Shin, L.M., Lasko, N.B., et al. (2009). **Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder.** *Biological Psychiatry*, 66, 1075-1082. doi:10.1016/j.biopsych.2009.06.026 *Background:* A clinical characteristic of PTSD is persistently elevated fear responses to stimuli associated with the traumatic event. The objective herein is to determine whether extinction of fear responses is impaired in PTSD and whether such impairment is related to dysfunctional activation of brain regions known to be involved in fear extinction, viz., amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), and dACC. *Methods:* Sixteen individuals diagnosed with PTSD and 15 trauma-exposed non-PTSD control subjects underwent a 2-day fear conditioning and extinction protocol in a 3-T functional magnetic resonance imaging scanner. Conditioning and extinction training were conducted on Day 1. Extinction recall (or extinction memory) test was conducted on Day 2 (extinguished conditioned stimuli presented in the absence of shock). Skin conductance response (SCR) was scored throughout the experiment as an index of the conditioned response. *Results:* The SCR data revealed no significant differences between groups during acquisition and extinction of conditioned fear on Day 1. On Day 2, however, PTSD subjects showed impaired recall of extinction memory. Analysis of functional magnetic resonance imaging data showed greater amygdala activation in the PTSD group during Day 1 extinction learning. During extinction recall, lesser activation in hippocampus and vmPFC and greater activation in dACC were observed in the PTSD group. The magnitude of extinction memory across all subjects was correlated with activation of hippocampus and vmPFC during extinction recall testing. *Conclusions:* These findings support the hypothesis that fear extinction is impaired in PTSD. They further suggest that dysfunctional activation in brain structures that mediate fear extinction learning, and especially its recall, underlie this impairment.

Morgan, C.A., Wang, S., Southwick, S.M., Rasmusson, A., Hazlett, G., Hauger, R.L., et al. (2000). **Plasma neuropeptide-Y concentrations in humans exposed to military survival training.** *Biological Psychiatry*, 47, 902-909. doi:10.1016/S0006-3223(99)00239-5 *Background:* NPY is present in extensive neuronal systems of the brain and is present in high concentrations in cell bodies and terminals in the amygdala. Preclinical studies have shown that injections of NPY into the central nucleus of the amygdala function as a central anxiolytic and buffer against the effects of stress. The objective of this study was to assess plasma NPY immunoreactivity in healthy soldiers participating in high intensity military training at the US Army survival school. The Army survival school provides a means of observing individuals under high levels of physical, environmental, and psychological stress, and consequently is considered a reasonable analogue to stress

incurred as a result of war or other catastrophic experiences. *Methods:* Plasma levels of NPY were assessed at baseline (prior to initiation of training), and 24 hours after the conclusion of survival training in 49 subjects, and at baseline and during the Prisoner of War (POW) experience (immediately after exposure to a military interrogation) in 21 additional subjects. *Results:* Plasma NPY levels were significantly increased compared to baseline following interrogations and were significantly higher in Special Forces soldiers, compared to non-Special Forces soldiers. NPY elicited by interrogation stress was significantly correlated to the subjects' behavior during interrogations and tended to be negatively correlated to symptoms of reported dissociation. Twenty-four hours after the conclusion of survival training, NPY had returned to baseline in Special Forces soldiers, but remained significantly lower than baseline values in non-Special Forces soldiers. NPY was positively correlated with both cortisol and behavioral performance under stress. NPY was negatively related to psychological symptoms of dissociation. *Conclusions:* These results provide evidence that uncontrollable stress significantly increases plasma NPY in humans, and when extended, produces a significant depletion of plasma NPY. Stress-induced alterations of plasma NPY were significantly different in Special Forces soldiers compared to non-Special Forces soldiers. These data support the idea that NPY may be involved in the enhanced stress resilience seen in humans.

Neumeister, A., Normandin, M.D., Pietrzak, R.H., Piomelli, D., Zheng, M.Q., Gujarró-Anton, A., et al. (2013). **Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: A positron emission tomography study.** *Molecular Psychiatry*, 18, 1034-1040. doi:10.1038/mp.2013.61 Endocannabinoids and their attending CB1 receptor have been implicated in animal models of PTSD. However, their specific role has not been studied in people with PTSD. Herein, we present an *in vivo* imaging study using PET and the CB1-selective radioligand [(11)C]OMAR in individuals with PTSD, and healthy controls with lifetime histories of trauma (trauma-exposed controls (TC)) and those without such histories (healthy controls (HC)). Untreated individuals with PTSD ( $N = 25$ ) with non-combat trauma histories, and TC ( $N = 12$ ) and HC ( $N = 23$ ) participated in a magnetic resonance imaging scan and a resting PET scan with the CB1 receptor antagonist radiotracer [(11)C]OMAR, which measures the volume of distribution (VT) linearly related to CB1 receptor availability. Peripheral levels of anandamide, 2-arachidonoylglycerol, oleylethanolamide, palmitoylethanolamide and cortisol were also assessed. In the PTSD group, relative to the HC and TC groups, we found elevated brain-wide [(11)C]OMAR VT values ( $F(2,53)=7.96$ ,  $p = 0.001$ ; 19.5% and 14.5% higher, respectively), which were most pronounced in women ( $F(1,53)=5.52$ ,  $p = 0.023$ ). Anandamide concentrations were reduced in the PTSD relative to the TC (53.1% lower) and HC (58.2% lower) groups. Cortisol levels were lower in the PTSD and TC groups relative to the HC group. Three biomarkers examined collectively—OMAR VT, anandamide and cortisol—correctly classified nearly 85% of PTSD cases. These results suggest that abnormal CB1 receptor-mediated anandamide signaling is implicated in the etiology of PTSD, and provide a promising neurobiological model to develop novel, evidence-based pharmacotherapies for this disorder.

Pitman, R.K., Orr, S.P., Forgue, D.F., deJong, J.B., & Claiborn, J. M. (1987). **Psychophysiological assessment of posttraumatic stress disorder imagery in Vietnam combat Veterans.** *Archives of General Psychiatry*, 44, 970-975. doi:10.1001/archpsyc.1987.01800230050009

This study used psychophysiological techniques to assess emotional arousal during imagery of psychologically traumatic experiences. All subjects were medication-free Vietnam combat Veterans, classified on the basis of *DSM-III-R* criteria into groups with PTSD ( $n = 18$ ) and no mental disorder (control,  $n = 15$ ), which did not differ in extent of combat or in the judged severity of the traumatic experiences reported. "Scripts" describing each subject's combat experiences as well as other experiences were read to them in the laboratory, and they were instructed to imagine the events the scripts portrayed, while heart rate, skin conductance, and frontalis electromyogram were recorded. The PTSD subjects' physiologic responses to their combat scripts were markedly higher than the controls'. The combined physiologic variables identified PTSD subjects with a specificity of 100% and a sensitivity of 61%. The results demonstrate exaggerated physiologic arousal during recollection of traumatic experiences in PTSD.

Pitman, R K., Rasmusson, A.M., Koenen, K.C., Shin, L.M., Orr, S.P., Gilbertson, M.W., et al. (2012). **Biological studies of post-traumatic stress disorder.** *Nature Reviews Neuroscience*, 13, 769-787.

doi:10.1038/nrn3339 PTSD is the only major mental disorder for which a cause is considered to be known: that is, an event that involves threat to the physical integrity of oneself or others and induces a response of intense fear, helplessness or horror. Although PTSD is still largely regarded as a psychological phenomenon, over the past three decades the growth of the biological PTSD literature has been explosive, and thousands of references now exist. Ultimately, the impact of an environmental event, such as a psychological trauma, must be understood at organic, cellular and molecular levels. This Review attempts to present the current state of this understanding on the basis of psychophysiological, structural and functional neuroimaging, and endocrinological, genetic and molecular biological studies in humans and in animal models.

Raskind, M.A., Peskind, E.R., Hoff, D.J., Hart, K.L., Holmes, H.A., Warren, D., et al. (2007). **A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat Veterans with post-traumatic stress disorder.** *Biological Psychiatry*, 61, 928-934. doi:10.1016/j.biopsych.2006.06.032

*Background:* Excessive brain responsiveness to norepinephrine appears to contribute to PTSD, particularly at night. Prazosin, a brain active alpha-1 adrenergic receptor antagonist, significantly reduced trauma nightmares and sleep disturbance in 10 Vietnam War combat Veterans in a previous placebo-controlled crossover study. The current parallel group trial in a larger sample of Veterans evaluated prazosin effects on trauma nightmares, sleep quality, global clinical status, dream characteristics, and comorbid depression. *Methods:* Forty Veterans (mean age  $56 \pm 9$ ) with chronic PTSD and distressing trauma nightmares and sleep disturbance were randomized to evening prazosin ( $13.3 \pm 3$  milligrams per day [mg/day]) or placebo for 8 weeks. *Results:* In the evaluable sample ( $n = 34$ ), primary outcome

measures demonstrated that prazosin was significantly superior to placebo for reducing trauma nightmares and improving sleep quality and global clinical status with large effect sizes. Prazosin shifted dream characteristics from those typical of trauma-related nightmares toward those typical of normal dreams. Blood pressure changes from baseline to end study did not differ significantly between prazosin and placebo. **Conclusions:** Prazosin is an effective and well-tolerated treatment for trauma nightmares, sleep disturbance and global clinical status in Veterans with chronic PTSD.

Rasmusson, A.M., Hauger, R.L., Morgan C.A., Bremner, J.D., Charney, D.S., & Southwick, S.M. (2000). **Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD.** *Biological Psychiatry*, 47, 526-539. doi:10.1016/s0006-3223(99)00185-7

**Background:** Consistent with many studies demonstrating enhanced reactivity of the sympathetic nervous system in PTSD, the administration of yohimbine, a noradrenergic  $\alpha$ 2-antagonist, has been shown to increase core symptoms of PTSD and to induce greater increases in plasma 3-methyl-4-hydroxy-phenyl-glycol (MHPG) in subjects with PTSD compared with healthy control subjects. In turn, NPY has been shown to inhibit the release of norepinephrine from sympathetic noradrenergic neurons. **Methods:** In the following study, plasma NPY responses to yohimbine and placebo were measured in a subgroup of 18 subjects with PTSD and 8 healthy control subjects who participated in the previous study of the effect of yohimbine on plasma MHPG. **Results:** The PTSD subjects had lower baseline plasma NPY and blunted yohimbine-stimulated increases in plasma NPY compared with the healthy control subjects. Within the PTSD group, baseline plasma NPY levels correlated negatively with combat exposure scale scores, baseline PTSD and panic symptoms, and yohimbine-stimulated increases in MHPG and systolic blood pressure. **Conclusions:** This study suggests that combat stress-induced decreases in plasma NPY may mediate, in part, the noradrenergic system hyperreactivity observed in combat-related PTSD. The persistence of this decrease in plasma NPY may contribute to symptoms of hyperarousal and the expression of exaggerated alarm reactions, anxiety reactions, or both in combat Veterans with PTSD long after war.

Rasmusson, A.M., Pinna, G., Paliwal, P., Weisman, D., Gottschalk, C., Charney D., et al. (2006). **Decreased cerebrospinal fluid allopregnanolone levels in women with posttraumatic stress disorder.** *Biological Psychiatry*, 60, 704-713. doi:10.1016/j.biopsych.2006.03.026

**Background:** Alterations in the  $\gamma$ -amino-butyric acid (GABA) neurotransmitter system have been identified in some populations with PTSD. **Methods:** To further investigate factors of relevance to GABAergic neurotransmission in PTSD, we measured CSF levels of allopregnanolone and pregnanolone combined (ALLO: congeners that potently and positively modulate effects of GABA at the GABAA receptor), 5LOdihydroprogesterone (5hydroprogesterone (5ners that potentiallopregnanolone), DHEA (a negative modulator of GABAA receptor function), and progesterone with gas chromatography, mass spectrometry in premenopausal women with ( $n = 9$ ) and without ( $n = 10$ ) PTSD. Subjects were free of psychotropic medications, alcohol, and

illicit drugs; all were in the follicular phase of the menstrual cycle except three healthy and four PTSD subjects receiving oral contraceptives. **Results:** There were no group differences in progesterone, 5 $\alpha$ -DHP, or DHEA levels. The PTSD group ALLO levels were < 39% of healthy group levels. The ALLO/DHEA ratio correlated negatively with PTSD re-experiencing symptoms ( $n = re\ werp < 008$ ; trend) and with Profile of Mood State depression/dejection scores ( $n = 008$ ;  $trp < 0008$ ). **Conclusion:** Low CSF ALLO levels in premenopausal women with PTSD might contribute to an imbalance in inhibitory versus excitatory neurotransmission, resulting in increased PTSD re-experiencing and depressive symptoms.

Rasmusson, A.M., Vasek, J., Lipschitz, D.S., Vojvoda, D., Mustone, M.E., Shi, Q., Gudmundsen, G., et al. (2004). **An increased capacity for adrenal DHEA release is associated with decreased avoidance and negative mood symptoms in women with PTSD.** *Neuropsychopharmacology*, 29,1546-1557. doi:10.1038/sj.npp.1300432

We recently found increased adrenal cortisol responses to ACTH1-24 and increased pituitary ACTH and adrenal cortisol responses to corticotropin-releasing factor in premenopausal women with chronic PTSD compared to healthy non-traumatized subjects. This pattern of HPA hyper-reactivity has been previously seen in healthy individuals treated with the antiglucocorticoid mifepristone. We therefore investigated whether endogenous plasma levels of antiglucocorticoids such as DHEA and progesterone were increased in premenopausal women with PTSD at baseline or in response to adrenal activation by ACTH1-24. The study revealed that DHEA responses to 250 microg ACTH1-24 were increased in 13 PTSD subjects compared to 13 healthy non-traumatized subjects, while DHEA levels were generally increased in the PTSD subjects compared to seven healthy traumatized subjects. Cortisol responses to ACTH1-24 were also higher in the women with PTSD, while progesterone levels and responses were not different among the three groups. In addition, among the PTSD subjects, the peak change in DHEA in response to ACTH1-24 was negatively correlated with the total Clinician Administered PTSD Scale score, while the peak DHEA to cortisol ratio was inversely associated with negative mood symptoms measured by the Profile of Mood States scale. This work suggests that an increased capacity for DHEA release in response to extreme adrenal activation may influence the pattern of HPA axis adaptation to extreme stress, as well as mitigate the severity of PTSD and negative mood symptoms in premenopausal women with PTSD.

Ressler, K.J., Mercer, K.B., Bradley, B., Jovanovic, T., Mahan, A., Kerley, K., et al. (2011). **Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor.** *Nature*, 470, 492-497. doi:10.1038/nature09856

PACAP is known to broadly regulate the cellular stress response. In contrast, it is unclear if the PACAP-PAC1 receptor pathway has a role in human psychological stress responses, such as PTSD. Here we find, in heavily traumatized subjects, a sex-specific association of PACAP blood levels with fear physiology, PTSD diagnosis and symptoms in females. We examined 44 SNPs spanning the PACAP (encoded by ADCYAP1) and PAC1 (encoded by ADCYAP1R1) genes, demonstrating a sex-specific association with PTSD. A single SNP in a putative oestrogen response

element within ADCYAP1R1, rs2267735, predicts PTSD diagnosis and symptoms in females only. This SNP also associates with fear discrimination and with ADCYAP1R1 messenger RNA expression in human brain. Methylation of ADCYAP1R1 in peripheral blood is also associated with PTSD. Complementing these human data, ADCYAP1R1 mRNA is induced with fear conditioning or oestrogen replacement in rodent models. These data suggest that perturbations in the PACAP-PAC1 pathway are involved in abnormal stress responses underlying PTSD. These sex-specific effects may occur via oestrogen regulation of ADCYAP1R1. PACAP levels and ADCYAP1R1 SNPs may serve as useful biomarkers to further our mechanistic understanding of PTSD.

Shalev, A.Y., Videlock, E.J., Peleg, T., Segman R., Pitman, R.K., & Yehuda, R. (2008). **Stress hormones and post-traumatic stress disorder in civilian trauma victims: A longitudinal study. Part I: HPA axis responses.** *International Journal of Neuropsychopharmacology*, *11*, 365-372. doi:10.1017/S1461145707008127 The aim of the study was to evaluate the association between PTSD and HPA axis responses to the triggering trauma. A companion paper evaluates the adrenergic response and interactions between the two. We measured plasma and saliva cortisol, hourly urinary excretion of cortisol, plasma levels of ACTH, and the leukocyte glucocorticoid receptor (GR) density of 155 non-injured survivors of traumatic events (91 males and 64 females; 125 road traffic accidents, 19 terrorist attacks, 11 others). Measurements were taken during survivors' admissions to an emergency room (ER) of a general hospital; in the mornings; and 10 days, 1 month, and 5 months later. Symptoms of peritraumatic dissociation, PTSD, and depression were assessed on each follow-up session. The clinician-administered PTSD scale (CAPS) conferred a diagnosis of PTSD at 5 months. Survivors with ( $n = 31$ ) and without ( $n = 124$ ) PTSD at 5 months had similar levels of hormones at all times. Plasma cortisol levels decreased with time in both groups. Female subjects had lower ACTH levels than males. PTSD in females was associated with higher levels of ACTH. In unselected cohorts of trauma survivors, PTSD is not preceded by a detectable abnormality of peripheral HPA axis hormones.

Shin, L.M., Bush, G., Milad, M.R., Lasko, N.B., Brohawn, K.H., Hughes, K.C., et al. (2011). **Exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: A monozygotic twin study of posttraumatic stress disorder.** *American Journal of Psychiatry*, *168*, 979-985. doi:10.1176/appi.ajp.2011.09121812 *Objective:* Neuroimaging studies have revealed functional abnormalities in the anterior cingulate cortex in PTSD. The goal of this study was to determine whether hyperresponsivity of the dorsal anterior cingulate in PTSD is an acquired characteristic or a familial risk factor. *Method:* Using a case-control twin design, the authors studied combat-exposed Veterans with PTSD ( $N = 12$ ) and their identical combat-unexposed co-twins ( $N = 12$ ), as well as combat-exposed Veterans without PTSD ( $N = 14$ ) and their identical combat-unexposed co-twins ( $N = 14$ ). Participants underwent functional MRI during completion of the Multi-Source Interference Task, which reliably activates the dorsal anterior cingulate. *Results:* Combat-exposed Veterans with PTSD and

their unexposed co-twins had significantly greater activation in the dorsal anterior cingulate and tended to have larger response time difference scores, as compared to combat-exposed Veterans without PTSD and their co-twins. Dorsal anterior cingulate activation in the exposed twins was positively correlated with their PTSD symptom severity. Dorsal anterior cingulate activation in the unexposed twins was positively correlated with their combat-exposed co-twins' PTSD symptom severity, but not with depression or alcohol use severity in the combat-exposed co-twins. *Conclusions:* Hyperresponsivity in the dorsal anterior cingulate appears to be a familial risk factor for the development of PTSD following psychological trauma.

Southwick, S.M., Krystal, J.H., Bremner, J.D., Morgan, C.A., Nicolaou, A.L., Nagy, L.M., et al. (1997). **Noradrenergic and serotonergic function in posttraumatic stress disorder.** *Archives of General Psychiatry*, *54*, 749-758. doi:10.1001/archpsyc.1997.01830200083012 *Background:* Yohimbine hydrochloride produces marked behavioral and cardiovascular effects in combat Veterans with PTSD. In the present study, yohimbine was used as a probe of noradrenergic activity, and meta-chlorophenylpiperazine (m-CPP) as a probe of serotonergic activity. To our knowledge, this is the first study to describe the behavioral and cardiovascular effects of meta-CPP in patients with PTSD, and to compare these effects with those of yohimbine. *Method:* Twenty-six patients with PTSD and 14 healthy subjects each received an intravenous infusion of yohimbine hydrochloride (0.4 mg/kg), m-CPP (1.0 mg/kg), or saline solution on 3 separate test days in a randomized balanced order and in double-blind fashion. Behavioral and cardiovascular measurements were determined at multiple times. *Results:* Eleven (42%) of the patients with PTSD experienced yohimbine-induced panic attacks and had significantly greater increases compared with controls in anxiety, panic, and PTSD symptoms, but not in cardiovascular measurements. Eight patients (31%) with PTSD experienced m-CPP-induced panic attacks and had significantly greater increases compared with controls in anxiety, panic, and PTSD symptoms, and in standing diastolic blood pressure. Yohimbine-induced panic attacks tended to occur in different patients from m-CPP-induced panic attacks. *Conclusion:* These data suggest the presence of two neurobiological subgroups of patients with PTSD, one with a sensitized noradrenergic system, and the other with a sensitized serotonergic system.

Southwick, S.M., Krystal, J.H., Morgan, C.A., Johnson, D., Nagy, L.M., Nicolaou, A., et al. (1993). **Abnormal noradrenergic function in posttraumatic stress disorder.** *Archives of General Psychiatry*, *50*, 266-274. doi:10.1001/archpsyc.1993.01820160036003 To evaluate possible abnormal noradrenergic neuronal regulation in patients with PTSD, the behavioral, biochemical, and cardiovascular effects of intravenous yohimbine hydrochloride (0.4 mg/kg) were determined in 18 healthy male subjects and 20 male patients with PTSD. A subgroup of patients with PTSD were observed to experience yohimbine-induced panic attacks (70% [14/20]) and flashbacks (40% [8/20]), and they had larger yohimbine-induced increases in plasma 3-methoxy-4-hydroxyphenylglycol levels, sitting systolic blood pressure, and heart rate than those in healthy subjects. In addition, in the patients with PTSD,

yohimbine induced significant increases in core PTSD symptoms, such as intrusive traumatic thoughts, emotional numbing, and grief. These data were consistent with a large body of preclinical data that indicated that uncontrollable stress produces substantial increases in noradrenergic neuronal function. We discuss the implications of these abnormalities in noradrenergic functional regulation in relation to the long-term neurobiological sequelae of severe uncontrollable stress and the pathophysiological relationship between PTSD and other anxiety disorders, such as panic disorder.

Uddin, M., Aiello, A.E., Wildman, D.E., Koenen, K.C., Pawelec, G., de Los Santos, R., et al. (2010). **Epigenetic and immune function profiles associated with posttraumatic stress disorder.**

*Proceedings of the National Academy of Sciences of the United States of America*, 107, 9470-9475. doi:10.1073/pnas.0910794107

The biologic underpinnings of PTSD have not been fully elucidated. Previous work suggests that alterations in the immune system are characteristic of the disorder. Identifying the biologic mechanisms by which such alterations occur could provide fundamental insights into the etiology and treatment of PTSD. Here we identify specific epigenetic profiles underlying immune system changes associated with PTSD. Using blood samples ( $n = 100$ ) obtained from an ongoing, prospective epidemiologic study in Detroit, the Detroit Neighborhood Health Study, we applied methylation microarrays to assay CpG sites from more than 14,000 genes among 23 PTSD-affected and 77 PTSD-unaffected individuals. We show that immune system functions are significantly overrepresented among the annotations associated with genes uniquely unmethylated among those with PTSD. We further demonstrate that genes whose methylation levels are significantly and negatively correlated with traumatic burden show a similar strong signal of immune function among the PTSD affected. The observed epigenetic variability in immune function by PTSD is corroborated using an independent biologic marker of immune response to infection, CMV, a typically latent herpesvirus whose activity was significantly higher among those with PTSD. This report of peripheral epigenomic and CMV profiles associated with mental illness suggests a biologic model of PTSD etiology in which an externally experienced traumatic event induces downstream alterations in immune function by reducing methylation levels of immune-related genes.

Wolf, E.J., Rasmusson, A.M., Mitchell, K.S., Logue, M.W., Baldwin, C.T., & Miller, M.W. (2014). **A genome-wide association study of clinical symptoms of dissociation in a trauma-exposed sample.**

*Depression and Anxiety*, 31, 352-360. doi:10.1002/da.22260

*Background:* Recent work suggests that a subset of individuals with PTSD exhibit marked dissociative symptoms, as defined by derealization and depersonalization. A dissociative subtype of PTSD was added to the diagnostic criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders, Version 5 (DSM-5)* to capture this presentation of PTSD. This study examined genetic polymorphisms for association with the symptoms that define the dissociative subtype of PTSD using a genome-wide approach. *Methods:* The sample comprised 484 white, non-Hispanic, trauma-exposed Veterans and their partners who were assessed for lifetime PTSD and dissociation using a structured clinical

interview. The prevalence of PTSD was 60.5%. SNPs from across the genome were obtained from a 2.5 million SNP array. *Results:* Ten SNPs evidenced suggestive association with dissociation ( $P < 10^{-5}$ ). No SNPs met genome-wide significance criteria ( $P < 5 \times 10^{-8}$ ). The peak SNP was rs263232 ( $\beta = 1.4$ ,  $P = 6.12 \times 10^{-7}$ ), located in the adenylyl cyclase 8 (*ADCY8*) gene; a second SNP in the suggestive range was rs71534169 ( $\beta = 1.63$ ,  $P = 3.79 \times 10^{-6}$ ), located in the dipeptidyl-peptidase 6 (*DPP6*) gene. *Conclusions:* *ADCY8* is integral for long-term potentiation and synaptic plasticity and is implicated in fear-related learning and memory and long-term memory consolidation. *DPP6* is critical for synaptic integration and excitation. These genes may exert effects on basic sensory integration and cognitive processes that underlie dissociative phenomena.

Yehuda, R., Boisoeneau, D., Lowy, M.T., & Giller, E.L. (1995).

**Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat Veterans with and without posttraumatic stress disorder.**

*Archives of General Psychiatry*, 52, 583-593. doi:10.1001/archpsyc.1995.03950190065010

*Background:* Our previous studies have suggested that combat Veterans with PTSD have alterations in hypothalamic-pituitary-adrenal axis functioning that are different from the well-documented biological changes observed in major depressive disorder and following exposure to stress. *Methods:* In the present study, we examined cortisol and lymphocyte glucocorticoid receptor number before and after the administration of 0.50 and 0.25 mg of dexamethasone in 14 combat Veterans with PTSD, 12 combat Veterans without PTSD, and 14 non-psychiatric healthy men. All subjects were medication free at the time of testing and none met diagnostic criteria for major depression or substance dependence. *Results:* Combat Veterans with PTSD suppressed cortisol to a greater extent than did combat Veterans without PTSD and normal controls in response to both doses of dexamethasone. Differences in cortisol suppression could not be attributed to substance dependence history or differences in dexamethasone bioavailability. Combat Veterans with PTSD showed a larger number of baseline glucocorticoid receptors compared with normal men. Combat Veterans without PTSD also had a larger number of baseline glucocorticoid receptors compared with normal men and in fact were comparable to combat Veterans with PTSD on this measure. However, only Veterans with PTSD showed a decrease in lymphocyte glucocorticoid receptor number following dexamethasone administration. *Conclusion:* The data support the hypothesis of an enhanced negative feedback sensitivity of the hypothalamic-pituitary-adrenal axis in PTSD.

Yehuda, R., Pratchett, L.C., Elmes, M.W., Lehrner, A., Daskalakis, N.P., Koch, E., et al. (2014). **Glucocorticoid-related predictors and correlates of post-traumatic stress disorder treatment response in combat Veterans.**

*Interface Focus*, 4, 20140048. doi:10.1098/rsfs.2014.0048

The identification of biomarkers for PTSD and resilience/recovery is critical for advancing knowledge about pathophysiology and treatment in trauma-exposed persons. This study examined a series of glucocorticoid-related biomarkers prior to and in response to psychotherapy. Fifty-two male and female Veterans with PTSD were randomized 2 : 1 to receive either prolonged exposure (PE) therapy or a weekly MA

## FEATURED ARTICLES *continued*

intervention for 12 consecutive weeks. Psychological and biological assessments were obtained prior to and following treatment and after a 12-week naturalistic follow-up. Response was defined dichotomously as no longer meeting criteria for PTSD at post-treatment based on the Clinician Administered PTSD Scale for DSM-IV (CAPS). Clinical improvement on the CAPS was apparent for both PE and MA, with no significant difference according to treatment condition. Biomarkers predictive of treatment gains included the BCL1 polymorphism of the glucocorticoid receptor gene. Additional predictors of treatment response were higher bedtime salivary cortisol and 24 h urinary cortisol excretion. Pre-treatment plasma dehydroepiandrosterone/cortisol ratio and NPY levels were predictors of reductions in PTSD symptoms, and, for NPY only, of other secondary outcomes as well, including anxiety and depression ratings. Glucocorticoid sensitivity changed in association with symptom change, reflecting clinical state. It is possible to distinguish prognostic and state biomarkers of PTSD using a longitudinal approach in the context of treatment. Identified markers may also be relevant to understanding mechanisms of action of symptom reduction.

## ADDITIONAL CITATIONS

Abdallah, C.G., Salas, R., Jackowski, A., Baldwin, P., Sato, J.R., & Mathew, S.J. (in press). **Hippocampal volume and the rapid antidepressant effect of ketamine.** *Journal of Psychopharmacology*. doi:10.1177/0269881114544776 Although smaller hippocampal volumes predict poor treatment responses to monoaminergic antidepressants, this study showed that smaller hippocampal volume predicted enhanced responses to the glutamate-antagonist, ketamine, in depressed patients.

Baker, D.G., West, S.A., Nicholson, W.E., Ekhtor, N.N., Kasckow, J.W., Hill, K.K. et al. (1999). **Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat Veterans with posttraumatic stress disorder.** *American Journal of Psychiatry*, 156, 585-588. This study replicated findings of increased CSF CRF levels in males with PTSD; the study also found a relationship between low levels of urinary cortisol and severity of PTSD symptoms.

Cagetti, E., Pinna, G., Guidotti, A., Baicy, K., & Olsen, R.W. (2004). **Chronic intermittent ethanol (CIE) administration in rats decreases levels of neurosteroids in hippocampus, accompanied by altered behavioral responses to neurosteroids and memory function.** *Neuropharmacology*, 46, 570-579. doi:10.1016/j.neuropharm.2003.10.001 This study demonstrated deficits in the conversion of the allopregnanolone precursor (3 $\alpha$ -dihydroprogesterone) to allopregnanolone by the enzyme 3 $\alpha$ -hydroxysteroid dehydrogenase in model of binge alcohol consumption in male rodents, a pattern of findings similar to that demonstrated in women with PTSD without current substance abuse—suggesting convergence between environmental and intrinsic biological PTSD risk factors.

## ADDITIONAL CITATIONS *continued*

Friedman, M.J., & Davidson, J.R.T. (2014). **Pharmacotherapy for PTSD.** In M.J. Friedman, T.M. Keane, & P.A. Resick (Eds.), *Handbook of PTSD, science and practice (2nd ed.)*. (pp. 482-501). New York: Guilford Publications. This exhaustive review of pharmacotherapy studies in PTSD suggests the importance of developing medications that prevent or treat PTSD by targeting specific pathophysiological abnormalities associated with the disorder or sub-phenotypes of the disorder.

Galatzer-Levy, I.R., Karstoft, K.I., Statnikov, A., & Shalev, A.Y. (2014). **Quantitative forecasting of PTSD from early trauma responses: A Machine Learning application.** *Journal of Psychiatric Research*, 59, 68-76. doi:10.1016/j.jpsychires.2014.08.017 This study illustrates the advantage over data analytic techniques that rely on a *priori* hypothesis testing of new machine learning techniques that “learn from the data.”

Gill, J., Vythilingam, M., & Page, G.G. (2008). **Low cortisol, high DHEA, and high levels of stimulated TNF- $\alpha$ , and IL-6 in women with PTSD.** *Journal of Traumatic Stress*, 21, 530-539. doi:10.1002/jts.20372 Consistent with other studies suggesting that an increase in DHEA constitutes a protective adaptation to trauma, women with PTSD in this study had higher DHEA levels than trauma-exposed and non-exposed controls, but women with comorbid PTSD and major depression had lower morning DHEA levels, as well as lower DHEA/cortisol ratios and increased IL-6 levels.

Hill, M.N., Bierer, L.M., Makotkine, I., Golier, J.A., Galea, S., McEwen, B.S., et al. (2013). **Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks.** *Psychoneuroendocrinology*, 38, 2952-2961. doi:10.1016/j.psyneuen.2013.08.004 This study in individuals selected for their proximity to the World Trade Center attack found low blood levels of the endocannabinoid 2-AG, but not anandamide among participants with lifetime PTSD compared to those with no PTSD.

Karvonen, M.K., Valkonen, V.P., Lakka, T.A., Salonen, R., Koulu, M., Pesonen, U., et al. (2001). **Leucine7 to proline7 polymorphism in the preproneuropeptide Y is associated with the progression of carotid atherosclerosis, blood pressure and serum lipids in Finnish men.** *Atherosclerosis*, 159, 145-151. doi:10.1016/S0021-9150(01)00468-3 This seminal study found associations between a gene polymorphism conferring increases in NPY release during stress—thought to confer neuropsychological resilience to stress—and risk for long-term physical health consequences, pointing to future challenges in development of strategies to enhance both short- and long-term mental and physical health.

Kobayashi, I., & Mellman, T.A. (2012). **Gender differences in sleep during the aftermath of trauma and the development of posttraumatic stress disorder.** *Behavioral Sleep Medicine*, 10, 180-190. doi:10.1080/15402002.2011.654296 This first study to examine gender differences in sleep architecture in the aftermath of trauma found that women who developed PTSD had more sleep awakenings than men, and that women who developed PTSD exhibited less sleep than women who did not.

Kuo, L.E., Kitlinska, J.B., Tilan, J.U., Li, L., Baker, S.B., Johnson, M.D., et al. (2007). **Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome.** *Nature Medicine*, *13*, 803-811. doi:10.1038/nm1611

This high-profile study demonstrated that stress reduced weight in rodents, but stress combined with a high fat/high sugar diet markedly increased centripetal obesity and other stigmata of metabolic syndrome, mediated by actions of NPY at NPY-Y<sub>2</sub> receptors in abdominal fat—phenomena reversed by the local or systemic injection of an NPY-Y<sub>2</sub> receptor antagonist or local glucocorticoid antagonist.

Lanius, R.A., Brand, B., Vermetten, E., Frewen, P.A., Spiegel, D. (2012). **The dissociative subtype of posttraumatic stress disorder: Rationale, clinical and neurobiological evidence, and implications.** *Depression & Anxiety*, *29*, 701-708. doi:10.1002/da.21889 This review presents up-to-date evidence characterizing the neurobiological underpinnings and treatment outcomes related to the dissociative subtype of PTSD—characterized primarily by depersonalization and derealization symptoms in addition to other PTSD symptoms.

Levy-Gigi, E., Szabo, C., Kelemen, O., & Keri, S. (2013). **Association among clinical response, hippocampal volume, and FKBP5 gene expression in individuals with posttraumatic stress disorder receiving cognitive behavioral therapy.** *Biological Psychiatry*, *74*, 793-800. doi:10.1016/j.biopsych.2013.05.017 This study demonstrated reduced pretreatment FKBP5 gene expression and hippocampal volume in PTSD, abnormalities that normalized in association with positive response to CBT.

Mellman, T.A., Kumar, A., Kulick-Bell, R., Kumar, M., & Nolan, B. (1995). **Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD.** *Biological Psychiatry*, *38*, 174-179. doi:10.1016/0006-3223(94)00238-X This polysomnography study in unmedicated participants who also collected urine over 24 hours for norepinephrine and MHPG in three 8-hour epochs, demonstrated “non-diminished” nighttime noradrenergic activity in individuals with PTSD that correlated negatively with sleep disturbance.

Morgan, C.A., Rasmusson, A.M., Winters, B., Hauger, R.L., Morgan, J., Hazlett, G., et al. (2003). **Trauma exposure rather than posttraumatic stress disorder is associated with reduced baseline plasma neuropeptide-Y levels.** *Biological Psychiatry*, *54*, 1087-1091. doi:10.1016/S0006-3223(03)00433-5 This paper reported data from two studies: one of male Vietnam Veterans with PTSD and one of male active duty participants in survival training, to demonstrate the relationship between trauma exposure and reductions in plasma NPY.

Orr, S.P., Metzger, L.J., Lasko, N.B., Macklin, M.L., Hu, F.B., Shalev, A.Y., et al. (2003). **Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure: Association with posttraumatic stress disorder.** *Archives of General Psychiatry*, *60*, 283-288. doi:10.1001/archpsyc.60.3.283 This study in Vietnam combat Veterans and their non-combat exposed monozygotic twins showed that greater heart rate responses to sudden loud tones was an acquired trait related to PTSD rather than to combat exposure, and was not a familial vulnerability factor.

Phan, K.L., Wager, T., Taylor, S.F., & Liberzon, I. (2002). **Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI.** *Neuroimage*, *16*, 331-348. doi:10.1006/nimg.2002.1087 This meta-analysis compiled PET and fMRI data in healthy subjects to determine the neuroanatomical correlates of positive and negative emotions, including disgust, sadness, happiness, anger, and fear.

Rasmusson, A.M., Schnurr, P.P., Zukowska, Z., Scioli, E., & Forman, D.E. (2010). **Adaptation to extreme stress: Post-traumatic stress disorder, neuropeptide Y, and metabolic syndrome.** *Experimental Biology and Medicine*, *235*, 1150-1162. doi:10.1258/ebm.2010.009334 This review focused on the link between alterations in NPY system functioning, PTSD, and metabolic syndrome—as new studies emerged linking trauma exposure and PTSD to risk for metabolic syndrome as well as to cardiovascular system dysfunction.

Richards, A., Metzler, T.J., Ruoff, L.M., Inslicht, S.S., Rao, M., Talbot, L.S., et al. (2013). **Sex differences in objective measures of sleep in post-traumatic stress disorder and healthy control subjects.** *Journal of Sleep Research*, *22*, 679-687. doi:10.1111/jsr.12064 This laboratory electroencephalography (EEG) study in 83 unmedicated men and women with and without PTSD revealed differences in sleep architecture related both to gender and PTSD severity.

Sah, R., Ekhtor, N.N., Strawn, J.R., Sallee, F.R., Baker, D.G., Horn, P.S., et al. (2009). **Low cerebrospinal fluid neuropeptide Y concentrations in posttraumatic stress disorder.** *Biological Psychiatry*, *66*, 705-707. doi:10.1016/j.biopsych.2009.04.037 This study was the first to find low NPY levels in the cerebrospinal fluid of male Veterans with PTSD, replicating findings of low NPY in plasma.

Scioli-Salter, E.R., Forman, D.E., Otis, J.D., Gregor, K., Valovski, I., & Rasmusson, A.M. (in press). **The shared neuroanatomy and neurobiology of comorbid chronic pain & PTSD: Therapeutic implications.** *Clinical Journal of Pain*. doi:10.1097/AJP.000000000000115 This review provided details regarding shared neuroanatomic and multiple neurobiological substrates accounting for the high rates of comorbidity between chronic pain and PTSD, implicating the NPY, GABAergic neuroactive steroid, opiate and endocannabinoid systems.

Sekiguchi, A., Sugiura, M., Taki, Y., Kotozaki, Y., Nouchi, R., Takeuchi, H., et al. (2013). **Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress.** *Molecular Psychiatry*, *18*, 618-623. doi:10.1038/mp.2012.51 This elegant longitudinal study showed that reduced gray matter volume in the anterior cingulate cortex prior to trauma predicted PTSD development, while orbitofrontal cortex gray matter volume decreased following trauma among those who developed PTSD—highlighting the interplay between factors that confer PTSD vulnerability and the effects of persistent traumatic stress.

## ADDITIONAL CITATIONS *continued*

Thomaes, K., Dorrepaal, E., Draijer, N., Jansma, E.P., Veltman, D.J., van Balkom, A.J. (2014). **Can pharmacological and psychological treatment change brain structure and function in PTSD? A systematic review.** *Journal of Psychiatric Research*, 50, 1-15. [doi:10.1016/j.jpsychires.2013.11.002](https://doi.org/10.1016/j.jpsychires.2013.11.002) This review suggested that pharmacotherapy, but not psychotherapy, was associated with increases in hippocampal volume, while both treatment modalities changed regional brain activation—in some cases, in the direction of normalization.

Woodward, S.H., Arsenault, N.J., Murray, C. & Bliwise, D.L. (2000). **Laboratory sleep correlates of nightmare complaint in PTSD inpatients.** *Biological Psychiatry*, 48, 1081-1087. [doi:10.1016/S0006-3223\(00\)00917-3](https://doi.org/10.1016/S0006-3223(00)00917-3) In this polysomnography study of 63 unmedicated male Veterans, increased wake-after-sleep-onset was specifically associated with complaints of trauma-related nightmares, which were found to occur outside of normal REM sleep.

Yehuda, R., Brand, S.R., Golier, J.A., & Yang, R.K. (2006). **Clinical correlates of DHEA associated with post-traumatic stress disorder.** *Acta Psychiatrica Scandinavica*, 114, 187-193. [doi:10.1111/j.1600-0447.2006.00801.x](https://doi.org/10.1111/j.1600-0447.2006.00801.x) This study found that a higher plasma DHEA/cortisol ratio measured at baseline predicted greater PTSD recovery over time among male Vietnam combat Veterans.

Yehuda, R., Bierer, L.M. Sarapas, C., Makotkine, I., Andrew, R., & Seckl, J.R. (2009). **Cortisol metabolic predictors of response to psychotherapy for symptoms of PTSD in survivors of the World Trade Center attacks on September 11, 2001.** *Psychoneuroendocrinology*, 34, 1304-1313. [doi:10.1016/j.psyneuen.2009.03.018](https://doi.org/10.1016/j.psyneuen.2009.03.018) This study found reductions in the endocannabinoid 2-AG, but not anandamide (AEA) among individuals in close proximity to the World Trade Center attacks who had a lifetime history of PTSD compared to those with no PTSD.

Zhang, K., Rao, F., Miramontes-Gonzalez, J.P., Hightower, C.M., Vaught, B., Chen, Y., et al. (2012). **Neuropeptide Y (NPY) genetic variation in the human promoter alters glucocorticoid signaling, yielding increased NPY secretion and stress responses.** *Journal of the American College of Cardiology*, 60, 1678-1689. [doi:10.1016/j.jacc.2012.06.042](https://doi.org/10.1016/j.jacc.2012.06.042) This study used multiple techniques to show relationships between one common NPY gene promoter polymorphism that confers increased NPY release and resistance to glucocorticoid regulatory restraint and increases in blood pressure and cardiovascular resistance in association with decreases in cardiac output.

Zhou, Z., Zhu, G., Hariri, A.R., Enoch, M.A., Scott, D., Sinha, R., et al. (2008). **Genetic variation in human NPY expression affects stress response and emotion.** *Nature*, 452, 997-1001. [doi:10.1038/nature06858](https://doi.org/10.1038/nature06858) This elegant study demonstrated the relationship between loss-of-function NPY polymorphisms and susceptibility to amygdala hyperreactivity and negative emotional reactions.