The Stressed Brain in the 21st Century: Research Advances and Clinical Dimensions

Keynote Speakers: James S. Jackson (University of Michigan), Eric J. Nestler (Mount Sinai Medical Center). Presented by Weill Cornell Medical College, Clinical & Translational Science Center (CTSC) and Hunter College of the City University of New York. Reported by Farooq Ahmed

Overview

Overwhelming evidence implicates stress as the cause or precipitant of many health problems such as ulcers and high blood pressure. Less appreciated is the fact that stress exerts powerful affects over brain functions. For example, chronic stress is associated with increases in symptoms of depression, generalized anxiety disorder, and post-traumatic stress disorder.

The 25th Annual International Symposium of the Hunter College Center for Gene Structure and Function, held in New York City on March 16, 2012, brought together noted basic and clinical neuroscience researchers from the U.S. and abroad with the goal of advancing our understanding of maladaptive stress responses in order to improve treatments and outcomes.

The impact of stress as it relates to race, ethnicity, gender, and socioeconomic status was also a major focus. Moreover, basic and translational researchers discussed mechanisms of risk and resilience related to stress-induced disease and disability during development and in adulthood. Both the morning and afternoon sessions concluded with an extensive, moderated question and answer period. A poster session, which was open for submissions by the scientific community, also provided ample opportunity for discussion. Thus, the symposium provided an excellent opportunity for researchers, clinicians, and caregivers to advance their understating of the pervasive and damaging physiological insults of continued stress, a condition that is becoming more pervasive in our society.

Sponsorship

This conference and meeting report were made possible with support from the Weill Cornell Medical College, Clinical & Translational Science Center (CTSC), Hunter College of the City University of New York, the National Institutes of Health, National Institute on Minority Health and Health Disparities, Research Centers in Minority Institutions – 8 G12 MD007599-27(formerly G12-RR-003037), and the Clinical and Translational Science Awards – 2UL1TR000457-06.
Introduction

Stress and Health Disparities

The morning session began with James Jackson of the University of Michigan who investigates the causes of a curious health disparity: That African Americans and non-Hispanic whites have radically different rates of physical and mental health disorders that occur over their lifetime. He said that although African Americans often live in stressful environments, their rates of stress-related mental health issues are lower than the rates seen for whites. However, African Americans’ rates of chronic physical health problems like diabetes, obesity, and cardiovascular disorders are higher. One motivation, Jackson noted, is that individuals will adopt health damaging behaviors in order to help them cope with their stressors so they do not experience cognitive disorders.

A Translational Approach

Following Jackson, Australian National University’s Julio Licinio presented information on the interactions between depression and obesity as chronic stress has been shown to play a role in both conditions. Depression and obesity affect 25 percent of people worldwide and both are major public health problems. Antidepressants, Licinio found, can lead to lifelong weight gain even after their use is discontinued. Parallel clinical and population health studies are being pursued to translate these findings.

Stress and Cellular Aging

Elissa Epel of the University of California, San Francisco, studies the effects of stress at a cellular level. She observed that telomere length, which serves as a clock on a cell’s life, can reflect exposure to trauma early in life. This may be overturned, however as some studies have shown that behavioral and psychological interventions can increase telomerase activity, which is the enzyme that lengthens telomeres.

Sex Differences

Because stress-related depression and anxiety disorders—including generalized anxiety, major depression, PTSD, social phobia, and panic disorder—occur at least twice as frequently in women as in men, Weill Cornell Medical College’s Margaret Altemus’s research focuses on sex differences in psychiatric disorders. She noted that increases in corticotrophin-releasing hormone could be a mechanism contributing to depression during pregnancy, while androgen hormones may play a role in premenstrual dysphoric disorder.

Genetic Mechanisms of Depression

The afternoon session began with a talk by Eric Nestler of Mount Sinai Medical Center who has been studying transcriptional and epigenetic changes that occur in a mouse model of chronic stress. Although depression is a relatively common syndrome, current treatments for depression only help about half of all patients, he said. Mouse models of depression show increased production of brain-derived neurotropic factor in the nucleus accumbens, and transcription factors mediate many of the long-lasting effects of stress in the brain and provide insight into novel therapeutic targets.
Developmental Psychobiology of Risk for Stress

Anxiety and stress related disorders peak during adolescence, affecting as many as 1 in 20 of youth, but 40 to 50 percent of patients do not respond to standard cognitive behavioral therapy. Weill Cornell Medical College’s BJ Casey is using human imaging and mouse genetics to help inform for whom and when such treatments are most effective. She uncovered an imbalance between emotion reactive and emotion regulation centers of the brain during adolescence, and said that genetic and environmental factors may increase this imbalance, but that genetic testing may inform and personalize treatment.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is one of the few mental illnesses defined on the basis of a causal event rather than on the basis of phenomenology. The cause is a psychological trauma that results from an event that threatens physical injury or death, such as exposure to war and combat, sexual abuse, or even being in a car accident. For the past three decades, Harvard Medical School’s Roger Pitman has investigated the biological changes that eventuate into PTSD. Sufferers, he has found, have an inadequate activation of inhibitory areas of the brain as well as over-activation of excitatory areas for the fear response. Both acquired and familial biomarkers have been identified in PTSD patients.

Sex and Age in Neural Responses to Stress

The symposium concluded with a talk by Hunter College’s Victoria Luine, who cautioned that research on stress has not fully taken into account sex differences in responses. She explained that much of the research done in the past only looked at adult male animals—whether humans, rats, or other species. Her research investigates the different ways in which male and female animals respond to stress. Luine has found that male, but not female rats, were impaired on spatial memory-related tasks after being stressed. Alcohol helped male rats cope with the effects of stress, but did not help female animals.

Environmental Affordances Framework of Health Disparities

Speaker:
James Jackson, University of Michigan

Highlights:
- African Americans have higher rates of physical health disorders than non-Hispanic whites but lower rates of mental health illnesses.
- This disparity begins in middle age and accelerates throughout life.
- Poor health behaviors such as smoking and drinking may buffer African American’s from developing mental health disorders until very late in life.

African Americans and non-Hispanic whites have radically different rates of physical and mental health disorders that occur over their lifetime. Although African Americans often live in stressful environments, their rates of stress-related mental health issues like major depression are lower than the rates seen for whites. However, African Americans’ rates of chronic physical health problems like diabetes, obesity, and cardiovascular disorders are higher. This disparity begins in middle age and leads to shorter lifespans—on average seven years or so shorter than their non-Hispanic white counterparts.
James Jackson of the University of Michigan investigates the causes of this disparity and seeks to understand the health outcomes. One big motivation, he says, is that individuals will adopt health damaging behaviors in order to help them cope with their stressors so they do not experience cognitive disorders.

African Americans, Jackson says, often have stressful living conditions such as poor housing. In many predominantly African American neighborhoods, fast food restaurants and liquor stores are more prevalent than grocery stores or gyms. Thus, from an early age they can cope with their stressors by eating comfort foods and self-medicating through alcohol, drugs, and by smoking.

Jackson argues that the “law of small effects” plays a key role in racial disparities—no one single factor produces the observed physical and mental health racial group disparities. Instead, many small factors interacting together create a significant overall difference, and these include environmental factors, but also genetics, culture, and social behaviors. Non-Hispanic whites generally have access to greater material and social support than non-whites and are therefore better able to resist stressors over the course of their lives, which accounts for the observed racial differences in the effects of coping with stress.

These differences lead to the epidemiological paradox noted above: Disparities in physical health favor whites over African Americans, but despite living in stressful environments, disparities in mental health generally favor African Americans over whites. In fact, early in their lives, African Americans have lower rates for physical ailments as well, but as they approach middle age, their rates accelerate greatly. African Americans’ poor health behaviors parallel this disparity: Unlike their non-Hispanic white counterparts, they tend to increase rates of smoking and alcohol use, for example, as they get older—whereas whites tend to decrease these behaviors. In addition, whites with increased poor health behaviors have higher rates of stress-related mental health issues than do African Americans. The converse is true for African Americans: Poor health behaviors buffer against mental health disorders later in life.

Why then, Jackson asks, do mental health disparities not increase for African Americans. Why does this disparity favor African Americans?

He says that coping strategies like the poor health behaviors have an immediate effect to reduce the activation of the stress-response network. For African Americans, this mechanism becomes a conditioned learned response to the noxious stimulus of stress. These behaviors may interfere with or mask the physiological cascade of stressful responses through the hypothalamic-pituitary-adrenal cortical (HPA) axis that ordinarily would eventuate in serious mental disorders. Long term, chronic activation of the HPA axis may be related to the etiology of some anxiety-related mental disorders. For example, eating comfort foods, which are high in fats and carbohydrates, may actually shutdown the stress response by inhibiting the release of corticotropin-releasing factor.

In addition, Jackson points out that alcohol, nicotine, and drug use stimulate the release of dopamine and beta-endorphins, which diminishes the stress response and leads to feelings of relaxation. These drugs may also further activate the HPA axis; thus, individuals may be psychologically released from stress, although they are not physically released from the effects of stress.

Jackson concludes that behavioral coping strategies, in the face of chronic stressful conditions, may be effective in “preserving” African American mental health, but may simultaneously contribute, along with structural inequalities like poor living conditions, and stressful life conditions, to observed disparities in physical health morbidity and mortality.
Translational Approaches to the Shared Biology of Stress, Depression, and Obesity

Speaker:
Julio Licinio, Australian National University

Highlights:
- Depression and obesity affect 25 percent of people worldwide.
- Stress can play a role in the development of both illnesses.
- Antidepressants can lead to lifelong weight gain even after their use is discontinued.

Depression and obesity are both major public health problems worldwide and affect nearly 25 percent of individuals in the developed world. Although they often co-exist in the same person, they are typically studied as distinct and unrelated conditions.

Depression itself is one of the most common and disabling disorders: 21 million Americans suffer from the illness, which are more people than live in the states of New York or Texas. Depression has the second highest disease burden in the developed world, and antidepressants represent the second most widely sold drug class in the U.S. Major depression affects key organs and systems, independently doubles the risk for coronary heart disease, and greatly increases the risk for type II diabetes.

Worldwide, the obesity epidemic has been attributed to reduced physical activity and an increased food intake. Because of the considerable clinical and biological overlap between depression and obesity, Australian National University’s Julio Licinio studies the interface between these two conditions.

He has discovered ten interrelationships between the two: Depression and obesity frequently co-exist in the same person; both disorders are substantial health problems worldwide; obesity can follow depression that occurred earlier in life; depressed mood can be a side effect of obesity treatments; weight gain and obesity can be a side effect of antidepressant treatments; several neuropeptidergic and neurotransmitter systems, involving molecules such as corticotropin-releasing hormone, neuropeptide Y, serotonin, norepinephrine, and leptin are involved in the regulation of mood as well as body weight; depression and obesity are important risk factors for cardiovascular disease; genetic polymorphisms may underlie the predisposition both to cardiovascular disease and to depression; drugs used in depression studies predominantly affect either serotonin or norepinephrine in the central nervous system; and obesity treatments include central inhibition of both serotonin and norepinephrine reuptake.

However, a large question remained unanswered: What is the relationship between the two and how does stress, which occurs in both depression and obesity, play a role? In fact, the most common phenotype of a chronically stressed individual, Licinio says, is to be both depressed and obese.

Research on German immigrants demonstrated the links between the three conditions: Depression, diabetes, and stress-produced cortisol levels were much higher in non-native German, Jewish immigrants to Germany after that country’s reunification in 1990. Russians who were German natives, however, only showed elevated levels of depression. Chronic stress, Licinio concludes, can lead to both depression and obesity-related disorders.

Treatment of depression or chronic stress with antidepressants also leads to weight gain, and Licinio’s group sought out the connections. After all, 164 million antidepressants were prescribed in the U.S. in
2009 alone, and the lifetime prevalence of exposure to this class of drugs is known to be very high as well.

Licinio took a molecular psychiatric approach, and his research demonstrated a new paradigm that he calls SAD for “stress-antidepressant-diet.” His group placed rats under chronic stress conditions. They then treated the animals with a short course of antidepressants, and shifted them to a high-fat diet. Antidepressant treated animals gained more weight than untreated animals, even though the course of the treatment had ended. The researchers postulate an epigenetic effect at work and caution that antidepressant exposure is a contributor to the obesity epidemic. Parallel clinical and population health studies are being pursued to translate these findings.

**Basic and Translational Studies on the Developmental Psychobiology of Risk for Anxiety and Stress Related Disorders**

**Speaker:**
Elissa Epel, University of California, San Francisco

**Highlights:**
- Telomeres can serve as clocks on a cell’s life: The shorter they are, the closer the cell is to the end of its life.
- Telomeres length also reflects life experience; shorter telomeres can result from exposure to trauma early in life.
- Small studies have shown that behavioral and psychological interventions can increase telomerase activity, the enzyme that lengthens telomeres.

Anxiety and stress related disorders peak during adolescence, affecting as many as 1 in 20 of youth. They are the most common psychiatric disorders for this age group. The only evidenced based behavioral treatment available is cognitive behavioral therapy, which identifies the source of the anxiety and desensitizes the individual to it. However, 40-50 percent of patients do not improve with this therapy. Weill Cornell Medical College’s BJ Casey and her colleagues are using human imaging and mouse genetics to help inform for whom and when such treatments are most effective.

Recent imaging work by her group led to the identification of a developmental period during which an individual is susceptible to pathological states of anxiety and/or resistance to standard treatments. They showed differential structural and functional maturity of emotion reactive (limbic) relative to emotion regulation (prefrontal) brain circuitry during adolescence. This imbalance in differential timing of development in fronto-limbic circuitry leads to greater susceptibility to emotion dysregulation during adolescence—a time when diagnosis of anxiety related disorders peak.

Casey and her colleagues examined the significance of environmental factors such as early adversity and stress on the brain and behavior. In one such study, they looked at the long-term neural correlates of early suboptimal rearing conditions—children adopted to the US from orphanages abroad—on later emotional development. They showed that adverse rearing conditions in the postnatal period associated with heightened limbic activity when suppressing attention to cues of threat in late childhood and adolescence. These studies suggest that individuals who experience adversity during this period, or who have experienced adversity or multiple traumas earlier in development, have altered fronto-limbic circuitry that may put them at risk for developing symptoms of anxiety or depression as teens or adults.
Parallel human and mouse studies by Casey’s group identified genetic factors that may underlie anxiety and treatment efficacy. They examined emotion learning in genetically altered mice and in humans with a common single nucleotide polymorphism (SNP) in the brain-derived neurotrophic factor (BDNF) gene that leads to a valine to methionine substitution at codon 66. This polymorphism is associated with impaired activity-dependent release of BDNF in the brain, treatment resistant forms of anxiety-like behavior, altered extinction learning in mice and humans, and altered prefrontal and limbic regions that increase an imbalance in the fronto-limbic circuitry.

Casey points out that this research has implications for treatment of anxiety disorder. Genetic testing, she says, may inform and personalize treatment. Furthermore, because of the developmental changes in the brain that takes place during adolescence, a treatment that failed to work at one point in a patient’s life may in fact work well after that date. Casey’s team is working to develop novel evidence-based behavioral interventions that go beyond the current standard of care.

**Sex Differences in Stress Responses and Psychiatric Disorders**

**Speaker:**
Margaret Altemus, Weill Cornell Medical College

**Highlights:**
- Depression and anxiety disorders are more common in women.
- Increases in corticotropin-releasing hormone could be a mechanism contributing to depression during pregnancy.
- Androgen hormones may play a role in premenstrual dysphoric disorder.

Stress-related depression and anxiety disorders occur at least twice as frequently in women as in men. These include generalized anxiety and major depression, but also PTSD, social phobia, and panic disorder. Weill Cornell Medical College’s Margaret Altemus’s research focuses on sex differences in psychiatric disorders.

Because there are many differences between men and women that can impact brain function, research on the biological mechanisms that may contribute to the increased rates of anxiety and depression in women has been difficult. These dissimilarities include: genotypic differences and in utero testosterone levels, to puberty and other life and reproductive events. In fact, until puberty rates of depression between boys and girls are comparable, but after puberty there is a dramatic increase in women. In contrast, rates of anxiety disorders are greater in pre-pubertal girls than boys. To complicate the research, differing environmental stressors also play a role in the progress of these disorders.

To date, no clear mechanisms have been identified. Altemus cautions that although sex differences in physiological stress responses have been well studied, it remains to be seen whether these differences play any role in the sex difference in rates of anxiety and depression.

Reproductive-related conditions, Altemus says, may provide a window onto these mechanisms. Her team studied postpartum depression, a condition thought to occur after childbirth. However, 30 to 50 percent of postpartum depression cases actually began during pregnancy, and Altemus’s group sought to identify differences between these groups. They found that 80 percent of women who were depressed during pregnancy had a prior history of depression. The women with depression that occurred postpartum experienced symptoms of a different nature; the postpartum depression was often
their first onset of depression for these women, and they had more violent thoughts, psychosis, and obsessive compulsive disorder than the women who experienced depression during pregnancy.

Hormone levels fluctuate greatly during pregnancy, and Altemus and colleagues examined the levels of corticotropin-releasing hormone (CRH), which is a major coordinator of stress responses in the brain and is produced in multiple regions. CRH is itself activated by stress, produces anxiety, and is elevated in PTSD and depression associated with childhood abuse.

During pregnancy, cerebrospinal fluid CRH levels are 30 percent higher than normal, possibly because of elevated levels of the hormone in blood plasma. CRH binding protein levels also decrease in cerebrospinal fluid, which further increases the effects of CRH. The rise in CRH during pregnancy plays important roles in fetal development and preparation for birth.

The clinical implications of elevated CRH levels may mean that women vulnerable to depression may tolerate the hormone less well and become depressed during pregnancy. The mechanism, Altemus points out, is not related to the sex hormones estrogen or progesterone, and thus CRH could be a biomarker for depression during pregnancy.

Another way to use sex differences to understand the mechanism of these illnesses is to study premenstrual dysphoric disorder (PMDD) or severe premenstrual syndrome (PMS). PMDD occurs in the second half of the menstrual cycle and is characterized by anger and irritability, and food cravings much higher than in typical PMS. Levels of estrogen, progesterone, and cortisol are all normal in PMDD patients.

Altemus’s research has focused instead on the role of androgen hormones such as testosterone, dihydrotestosterone, and androstenedione as they are known to promote irritability. These androgen hormones are metabolites of progesterone, which reaches high levels in the luteal phase of the menstrual cycle. In a trial of the androgen blocker flutamide, which typically is used to treat prostate cancer, patients with PMDD reported feeling better over a range of symptoms, including food cravings, irritability, and bloating.

Altemus emphasizes that a better understanding of the role of reproductive hormones in stress physiology and psychiatric illness is likely to lead to new approaches to prevention and treatment.

**Transcriptional and Epigenetic Mechanisms of Depression**

**Speaker:**
**Eric J. Nestler**, Mount Sinai Medical Center

**Highlights:**
- Current treatments for depression only help about half of all patients.
- Mouse models of depression show increased production of brain-derived neurotrophic factor in the nucleus accumbens.
- Transcription factors mediate many of the long-lasting effects of stress on the brain and provide insight into novel therapeutic targets.

Although depression is a relatively common syndrome, only about half of patients go into complete remission with available treatments. To develop new therapeutics, researchers are studying the
molecular mechanisms underlying depression. Eric Nestler of Mount Sinai Medical Center has been studying transcriptional and epigenetic changes that occur in a mouse model of chronic stress.

Nestler’s lab induces social defeat in genetically inbred mice by placing them with an aggressor mouse of a different line. After repeated confrontations, the inbred mouse exhibits classic symptoms of depression, including a decreased interest in pleasure, increased anxiety-like behavior, hyperactivity in the hypothalamic-pituitary-adrenal axis, disrupted circadian rhythms, increased addiction liability, metabolic syndrome, and profound social avoidance—similar to symptoms in depressed humans. Mice that witnessed this induced social defeat in other mice also exhibit similar depressive tendencies. Only a prolonged administration of antidepressants helped the mice recover from this induced depression-like syndrome.

A subset of these genetically identical mice, which Nestler’s group termed resilient, did not experience this vulnerability. The fact that the resilient mice were genetically identical to susceptible mice and were raised under common environmental exposures, suggests a possible role for epigenetic factors that modulate a susceptibility to depression, Nestler said.

As the limbic circuits of the brain are known to regulate mood, Nestler’s group focused on the nucleus accumbens (NAc) region, which is one of the most important reward circuits and is a well-studied target in addiction research. The NAc receives dopamine innervation from a region of the midbrain called the ventral tegmental area (VTA), and Nestler found that susceptible mice increased the production of brain-derived neurotrophic factor (BDNF) in VTA dopaminergic neurons that innervate the NAc. Resilient animals were able to cope, on the other hand, by upregulating potassium channels in VTA neurons and normalizing BDNF signaling.

Using gene expression microarrays, Nestler and colleagues identified genes up- or down-regulated in the VTA and NAc of susceptible and resilient mice. Resilience, it turned out, was an active process in these animals and activated or depressed a different set of genes than did susceptible animals. Antidepressants such as fluoxetine mimicked many of the effects of resiliency.

Nestler further identified two key transcription factors that play a role in susceptibility and resilience. The cAMP response element-binding (CREB) protein mediated susceptibility, while ΔFosB induction mediated resilience as well as antidepressant action. These transcription factors regulate gene expression at the chromatin level, with social defeat producing global changes in chromatin access through histone-modifying enzymes. This work lead Nestler to believe that pharmacological agents targeting these different enzymes might be used as novel treatments.

Nestler’s group also looked into the downstream effects of BDNF pathways. They found a concerted regulation of the WNT-DVL-GSK3 pathway in the NAc. The pathway was downregulated in susceptible animals as well as depressed humans, but upregulated in resilient animals. Pharmaceutical experience, however, suggests that GSK3 is not a good drug target because of its toxic side effects, and Nestler is looking into downstream targets as possible therapeutics to treat depression.

Basic and Translational Studies on the Developmental Psychobiology of Risk for Anxiety and Stress Related Disorders

Speaker:
BJ Casey, Weill Cornell Medical College
Highlights:
- Anxiety and stress disorders affect up to 1 in 20 youth, and 40 to 50 percent of patients do not respond to standard cognitive behavioral therapy.
- There is an imbalance between emotion reactive and emotion regulation centers of the brain during adolescence.
- Genetic and environmental factors may increase this imbalance, but genetic testing may inform and personalize treatment.

Anxiety and stress related disorders peak during adolescence, affecting as many as 1 in 20 of youth. They are the most common psychiatric disorders for this age group. The only evidenced based behavioral treatment available is cognitive behavioral therapy, which identifies the source of the anxiety and desensitizes the individual to it. However, 40-50 percent of patients do not improve with this therapy. Weill Cornell Medical College’s BJ Casey and her colleagues are using human imaging and mouse genetics to help inform for whom and when such treatments are most effective.

Recent imaging work by her group led to the identification of a developmental period during which an individual is susceptible to pathological states of anxiety and/or resistance to standard treatments. They showed differential structural and functional maturity of emotion reactive (limbic) relative to emotion regulation (prefrontal) brain circuitry during adolescence. This imbalance in differential timing of development in fronto-limbic circuitry leads to greater susceptibility to emotion dysregulation during adolescence--a time when diagnosis of anxiety related disorders peak.

Casey and her colleagues examined the significance of environmental factors such as early adversity and stress on the brain and behavior. In one such study, they looked at the long-term neural correlates of early suboptimal rearing conditions--children adopted to the US from orphanages abroad--on later emotional development. They showed that adverse rearing conditions in the postnatal period associated with heightened limbic activity when suppressing attention to cues of threat in late childhood and adolescence. These studies suggest that individuals who experience adversity during this period, or who have experienced adversity or multiple traumas earlier in development, have altered fronto-limbic circuitry that may put them at risk for developing symptoms of anxiety or depression as teens or adults.

Parallel human and mouse studies by Casey’s group identified genetic factors that may underlie anxiety and treatment efficacy. They examined emotion learning in genetically altered mice and in humans with a common single nucleotide polymorphism (SNP) in the brain-derived neurotrophic factor (BDNF) gene that leads to a valine to methionine substitution at codon 66. This polymorphism is associated with impaired activity-dependent release of BDNF in the brain, treatment resistant forms of anxiety-like behavior, altered extinction learning in mice and humans, and altered prefrontal and limbic regions that increase an imbalance in the fronto-limbic circuitry.

Casey points out that this research has implications for treatment of anxiety disorder. Genetic testing, she says, may inform and personalize treatment. Furthermore, because of the developmental changes in the brain that takes place during adolescence, a treatment that failed to work at one point in a patient’s life may in fact work well after that date. Casey’s team is working to develop novel evidence-based behavioral interventions that go beyond the current standard of care.
Studies of Identical Twins Discordant for Combat Exposure in Vietnam

Speaker:
Roger Pitman, Harvard Medical School

Highlights:
- PTSD can be the result of a wide variety of traumas, including exposure to war and combat, sexual abuse, or even being in a car accident.
- PTSD sufferers have an inadequate activation of inhibitory areas of the brain as well as over-activation of excitatory areas for the fear response.
- Both acquired and familial biomarkers have been found in PTSD sufferers.

Posttraumatic stress disorder (PTSD) is one of the few mental illnesses defined on the basis of a causal event rather than on the basis of phenomenology. The cause is a psychological trauma that results from an event that threatens physical injury or death. PTSD can be the result of a wide variety of potentially traumatic events, including exposure to war and combat, sexual abuse, or even being in a car accident. The person who experiences the event has an unconditioned response of intense fear, a sense of helplessness, or horror and then retains that fear long after the event has passed. Cross-sectional studies of biological markers for PTSD have been unable to reveal its origins.

For the past three decades, Harvard Medical School’s Roger Pitman has investigated the biological changes that eventuate into PTSD. His group pioneered a technique called script-driven imagery, in which a personal, traumatic combat narrative is presented to subjects who have experienced a requisite traumatic event, who either have PTSD or who do not (control subjects). This research was first done in veterans of the Vietnam War, and the researchers then measure physiological responses during mental imagery of the narrative.

Pitman and colleagues found that the veterans with PTSD had higher physiological responses to script-driven imagery, including increased heart rate, skin conductance and electromyogram activity. These results have been replicated in many types of trauma populations by other researchers.

Functional neuroimaging during script-driven imagery and other tasks has revealed that an area of the brain called the ventromedial prefrontal cortex had diminished reactivity in PTSD sufferers compared to individuals who had experienced a traumatic event but who did not develop the disorder. The ventromedial prefrontal cortex has been shown to inhibit the activity of the amygdala, which coordinates the fear response. Deficient activation of the ventromedial prefrontal cortex is the most widely replicated finding in PTSD neuroimaging studies.

Further work in Pitman’s lab demonstrated that extinction retention, or the ability not to respond to a fearful stimulus that is no longer relevant, is diminished in PTSD patients. The ventromedial prefrontal cortex regulates this ability as well. Other areas of the brain demonstrated differential responses in PTSD patients versus non-sufferers. The hippocampus showed a decreased activity during extinction retention, whereas the dorsal anterior cingulate cortex showed an increased response in PTSD. PTSD sufferers, Pitman says, have an inadequate activation of inhibitory areas of the brain as well as over-activation of excitatory areas for the fear response.

To search for acquired and inherited biomarkers of PTSD, his group also studied male identical twin pairs in which one of the twins experienced combat during the Vietnam War. Because the subjects were genetically identical, the researchers were able to gain a surrogate representation of the individual--but for the traumatic exposure.
Pitman's lab analyzed four groups in total: Combat-exposed individuals who developed PTSD and their “high-risk” co-twins, and combat-exposed individuals who did not develop PTSD and their “low-risk” co-twins. The scientists found acquired PTSD markers that included high levels of psychopathology on a psychiatric symptom checklist; an elevated heart rate response to startling tones; a failure to retain extinction of a conditioned fear response; and a lowering of ventromedial prefrontal cortex volume. The non-combat exposed co-twins of the PTSD sufferers did not have these markers.

However, Pitman also found several biomarkers that represent familial risk factors for PTSD, such as a decreased hippocampal volume and increased resting metabolism in the dorsal anterior cingulate cortex, which promotes the fear response and opposes the actions of the ventromedial prefrontal cortex. Further research identified a single nucleotide polymorphism in a gene called FKBP5 found to be associated with PTSD that may be partially responsible for the increased activity in the dorsal anterior cingulate cortex.

**Accounting for Sex and Age in Neural Responses to Stress**

**Speaker:**
Victoria Luine, Hunter College

**Highlights:**
- Research on stress has not fully taken into account sex differences in responses.
- Male, but not female rats, were impaired on spatial memory-related tasks after being stressed.
- Alcohol helped male rats cope with the effects of stress, but did not help female animals.

In 1976, Hans Selye conceptualized the brain’s response to stress. Until 1998 when Bruce McEwen posited the allostatic load concept of chronic stress, little had been done to update Selye’s work on biological stress. The allostatic load model views stress as a pathology produced by the combined effects of many internal and external stressors, such as genetics, environmental factors, experience, personal habits, and development.

Hunter College’s Victoria Luine cautions that these models and terminology require updating for the 21st century. She explains that much of the research done in the past only looked at adult male animals—whether humans, rats, or other species. Her research investigates the different ways in which male and female animals respond to stress. Because many psychological illnesses are precipitated by stress and have different incidences in men and women, disease etiology and treatment may need to be different as well, she argues. Depression and PTSD occur at higher rates in women, for example, yet the treatment for male and female patients remains largely the same.

To study the sex differences in stress, Luine uses a rat model of restraint stress. A rat is placed in a small container that does not immobilize the animal, but prevents it from moving around and thus causes a psychological stress. This model has been shown to mimic chronic stress in humans and increase cortisol production. Her group then gave the rats spatial learning tasks, such as the radial arm maze, and determined whether stress affected their abilities. At baseline, male rodents had a better spatial memory than female rodents and made fewer errors navigating the mazes. Chronic restraint stress, however, increased the errors of male rats, but actually improved the performance of female animals. Results with another spatial memory task called the object placement test reiterated these findings, in which female rats performed better after stressful conditions. Other, non-spatial memory
tasks, such as object recognition, demonstrated no sex difference and male and female rats performed equally after restraint stress.

A study of anxiety in rats also uncovered sex-specific differences. In an open field test, control male animals were more anxious than females, but following stress males became less anxious while females become more anxious, reiterating the sexually dimorphic pattern seen in spatial memory tasks.

Luine’s group and other researchers also examined mediators of stress in the brain, including monoamines like serotonin, dopamine, and norepinephrine. Using high pressure liquid chromatography, they looked into the three areas of the brain most commonly associated with the stress response and which mediate memory and mood: The medial prefrontal cortex, the hippocampus, and the amygdala. Stress enhanced serotonergic and dopaminergic activity in males whereas it depressed both activities in females in every region examined. These changes, posits Luine, could be responsible for the different incidence of depression or PTSD in women and men.

Her group also looked at alcohol’s effects on memory and learning. Whether male or female, rats self-medicated when given access to alcohol under stressful conditions. Luine’s team discovered that the drug had beneficial effects in male rats but not in females; alcohol reversed the effects of stress-induced anxiety and depression, but only in male animals. Luine argues that sex and age should be considered in the etiology and treatment of stress-related illnesses.

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University of Michigan
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James S. Jackson is the Daniel Katz Distinguished University Professor of Psychology, Professor of Health Behavior and Health Education, School of Public Health, and Director and Research Professor of the Institute for Social Research. He is the past Chair, Social Psychology Training Program and Director of the Research Center for Group Dynamics, the Program for Research on Black Americans, and the Center for Afroamerican and African Studies, all at the University of Michigan. He is past-Chair of the Section on Social, Economic, and Political Sciences (K) of the American Association for the Advancement of Science (AAAS). He is a former Chair of the Section on Social and Behavioral Sciences, and the Task Force on Minority Issues of the Gerontological Society of America, and the Committee on International Relations and the Association for the Advancement of Psychology of the American Psychological Association. He is a former National President of the Black Students Psychological Association and the Association of Black Psychologists. He is current President of the Society for the Psychological Study of Social Issues.

He served on the National Advisory Mental Health Council of the National Institute of Mental Health and the National Institute on Aging Advisory Council and the Board of Scientific Counselors of NIA. He was recently named to the NIH Advisory Council to the Director. He is a fellow of the Gerontological Society of America, Society of Experimental Social Psychology, American Psychological Association, Association of Psychological Sciences, International Demographic Association, and the American Association for the Advancement of Science. He is the recipient of the Distinguished Career Contributions to Research Award, Society for the Psychological Study of Ethnic Minority Issues, American Psychological Association, the James McKeen Cattell Fellow Award for Distinguished Career Contributions in Applied Psychology, the Association for Psychological Sciences, Presidential Citation, American Psychological Association, and the Medal for Distinguished Contributions in Biomedical Sciences, New York Academy of Medicine. He is an elected member of the Institute of Medicine of the National Academies of Sciences, and a Fellow of the American Academy of Arts and Sciences.

Eric Nestler, M.D., Ph.D.
Mount Sinai Medical Center
Website

Dr. Nestler is the Nash Family Professor of Neuroscience at the Mount Sinai School of Medicine in New York, where he serves as Chair of the Department of Neuroscience and Director of the Friedman Brain Institute. He received his B.A., Ph.D., M.D. degrees, and psychiatry residency training, from Yale University. He served on the Yale faculty from 1987-2000, where he was the Elizabeth Mears and House Jameson Professor of Psychiatry and Neurobiology, and Director of the Division of Molecular Psychiatry. He moved to Dallas in 2000 where he served as the Lou and Ellen McGinley Distinguished Professor and Chair of the Department of Psychiatry at The University of Texas Southwestern Medical Center until moving to New York in 2008. Dr. Nestler is a member of the Institute of Medicine and a Fellow of the American Academy of Arts and Sciences. The goal of Dr. Nestler’s research is to better understand the molecular mechanisms of addiction and depression based on work in animal models, and to use this information to develop improved treatments of these disorders.
Speakers

Julio Licinio, M.D., F.A.P.A
John Curtin School of Medicine Research at Australian National University
Website

Julio Licinio, M.D., F.A.P.A., is Professor and Director of the John Curtin School of Medicine at the Australian National University, and head of the Department of Translational Medicine. He is also a Research Professor at the University of Southern California, in Los Angeles. Professor Licinio is originally from Brazil and lived for over 25 years in the United States, where he had clinical and research training in endocrinology and psychiatry at University of Chicago and Cornell. He then held academic positions at Yale, NIH, and UCLA, where he was Professor and Vice-Chair of Psychiatry and Director of the Center for Pharmacogenomics. Prior to moving to Australia, he was Miller Professor, Chairman of Psychiatry and Associate Dean at University of Miami. His work on the fundamental endocrine and pharmacogenomic mechanisms at the interface of obesity and depression has been extensively funded by NIH, and it is highly cited in the scientific literature. Dr. Licinio is the Founding Editor of three Nature Publishing Group journals, he Pharmacogenomics Journal, Translational Psychiatry and Molecular Psychiatry, which has an Impact Factor of 15, the highest in its field worldwide.

Elissa S. Epel, Ph.D.
University of California, San Francisco
Website

Elissa Epel is an Associate Professor in the Department of Psychiatry at UCSF. Dr. Epel received her training in psychology from Stanford and Yale University, with a focus on health psychology and behavioral medicine, and subsequently completed clinical training, focusing on behavioral medicine, at the Palo Alto Veterans Administration Health Care System, and a postdoctoral fellowship (in Psychology and Medicine) at UCSF. She is a faculty member of the Health Psychology program, the UCSF Osher Center for Integrative Medicine, the Robert Wood Johnson Health and Society Scholars fellowship program, the Assistant Director of the Center for Health and Community, and Director of Research for the UCSF Center on Obesity.

She has interests in the impact of stress physiology on ‘metabolic health,’ including food intake, insulin resistance, obesity, and premature aging at the cellular level, and how health enhancing interventions might enhance regulation in these systems. Along with Elizabeth Blackburn and colleagues, she demonstrated novel links between stress and stress arousal with markers of cellular aging (telomere length and telomerase activity). She aims to understand, from a psychological and biological perspective, why some people are vulnerable and others are resilient to chronic stress, and how much of accelerated aging is due to changes in metabolism and eating behavior. She focuses on mothers of children with chronic conditions, mainly autism, and older people caring for family members with dementia. She is also involved in clinical trials examining how stress reduction interventions might reverse or slow cellular aging.

Margaret Altemus, M.D.
Weill Cornell Medical College
Website

Margaret Altemus, M.D. is an Associate Professor of Psychiatry and Complementary and Integrative Medicine at the Weill Medical College of Cornell University in Manhattan. Dr. Altemus had clinical and
research training in psychiatry at Yale and the NIH Intramural Research Program before coming to Cornell. Dr. Altemus directs a neuroendocrinology research laboratory focused on the physiological interplay between stress, reproductive hormones, and affective disorders. She also is the director of the Payne Whitney Women’s Program, which provides clinical care and clinical training in addition to research in reproductive-related psychiatric disorders. Dr. Altemus is the Core Director of the Participant and Clinical Interactions Resource of the Weill Cornell CTSC.

**BJ Casey, Ph.D.**  
Weill Cornell Medical College  
[Website](#)

Dr. BJ Casey is the Sackler Professor for Developmental Psychobiology. She holds appointments in the Departments of Psychiatry, Neurology, and Neuroscience at Weill Cornell Medical College and in the Department of Psychology at Cornell University. She directs the Sackler Institute and Neuroscience Graduate Program in addition to directing the NIMH funded Center for Brain, Genetic and Behavioral (CBGB) research across development.

Casey is a world leader in pediatric neuroimaging and its use in typical and atypical development. She skillfully uses brain imaging to uniquely examine transitions into and out of developmental periods, such as the period of adolescence. Her work is grounded in translational studies from rodent to human, developing models for several psychiatric disorders and potential treatments. She is a member of several advisory boards including the NIMH Board of Scientific Counselors, the Scientific Advisory Board for NARSAD, the National Research Council Board of Children, Youth and Families and Committee for Assessing Juvenile Justice Reform.

**Roger Pitman, M.D.**  
Massachusetts General Hospital  
[Website](#)

Dr. Pitman is a psychiatrist at Massachusetts General Hospital and Professor of Psychiatry at Harvard Medical School, Boston, MA. He served as a psychiatrist in the U.S. Navy during the Vietnam War and went on to complete a 30-year career in the Department of Veterans Affairs prior to moving to MGH. He is the recipient of the International Society for Traumatic Stress Studies’ Award for Outstanding Scientific Achievement in the field of PTSD and its Lifetime Achievement Award. Dr. Pitman’s research into the psychobiology of PTSD spans more than 25 years. He has more than 100 peer-reviewed publications on PTSD and more than 200 overall publications in the general psychiatric and medical literature. He has authored or co-authored numerous structural and functional neuroimaging studies of PTSD. For the past 15 years, he has been conducting a large-scale, psychobiologic investigation of a national sample of monozygotic twins discordant for combat exposure in Vietnam.

**Victoria Luine, Ph.D.**  
Hunter College, City University of New York  
[Website](#)

Dr. Luine is a Distinguished Professor of CUNY and holds appointments in the Dept. of Psychology and the Gene Center at Hunter College, The Graduate Center of CUNY and Rockefeller University. She is Director of the NIH funded RISE and SCORE Research Programs for students and faculty, respectively. She received her PhD in Pharmacology from SUNY at Buffalo and was a post-doctoral fellow and faculty member at Rockefeller University before joining Hunter College in 1987. Luine’s research, primarily in animal models, has shown that hormones of adrenal and gonadal origin alter neural function and contribute to changes in cognition and mood over the lifespan. Of particular
interest is understanding how gonadal hormones, estradiol in females and testosterone in males, contribute to sex differences in responses to stress, psychoactive drugs and the aging process. She has served on numerous government and private review and advisory panels and is currently Secretary of the Federation of Associations in Brain and Behavioral Sciences and Chair of the Membership Comm. for the Organization for the Study of Sex Differences. Prof. Luine has received the CUNY Chancellor’s Award numerous times as well as an Outstanding Woman Scientist award from the Association for Women in Science and the Society for Neuroscience’s Bernice Grafstein Award for Mentoring in 2009.