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Bipolar Network News

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Mild Traumatic Brain Injury and Deployment Associated with Inflammatory Abnormalities in Veterans of the Iraq and Afghanistan Wars

Traumatic brain injury from improvised explosive devices is an injury particular to veterans of the wars in Iraq and Afghanistan. As has been seen in some athletes who sustain repeated mild traumatic brain injuries, such as boxers and football players, neurodegenerative dementias such as chronic traumatic encephalopathy can follow these concussions. Researchers are hoping to identify biomarkers that would help in the diagnosis and monitoring of repeated blast-induced traumatic brain injury. Researcher Elaine Peskind and colleagues have determined that both deployment to these wars and mild traumatic brain injuries received there are associated with increased inflammatory cytokines in cerebrospinal fluid.

In the study, veterans who had been deployed to Iraq or Afghanistan and had received mild traumatic brain injuries were compared to veterans who were deployed but who were not similarly injured and community participants who had neither been deployed nor experienced a brain injury. The average number of concussion-inducing blasts veterans in the first group had experienced was 14, with the latest occurring an average of four years prior to the study.

Inflammatory cytokine IL-7 was elevated in the spinal fluid of those veterans who had sustained brain injuries. IL-6 was higher both in those deployed and in those who sustained blasts. Eotaxin and granulocyte colony stimulating factor were higher in all of the veterans who had been deployed.

These cytokine abnormalities could account for behavior and cognitive difficulties associated with traumatic brain injury. The researchers concluded that both deployment and mild traumatic brain injury were associated with neural damage and neuroimmune responses.

Editor's Note: Michael E. Hoffer et al. reported in the journal PLosOne *in 2013 that veterans with blast-induced mild traumatic brain injury had a better acute outcome when they were given the antioxidant N-acetylcysteine (NAC) within the first 24 hours after the trauma. It is interesting to speculate whether this could be explained by NAC's anti-inflammatory effects, its enhancement of another antioxidant (glutathione), or its ability to increase glial glutamate transporters.*

Researcher Dewleen Baker reported in a personal communication to this editor (Robert Post) that in her patients, traumatic brain injury was also associated with white matter abnormalities, and that these injuries conveyed an increased risk of developing PTSD as well.

PANS, an Inflammatory Disease with Psychiatric Symptoms in Kids

Researcher Kiki Chang discussed pediatric acute onset neuropsychiatric syndrome (PANS), an inflammatory illness with psychiatric symptoms, at the 2014 meeting of the American Academy of Child and Adolescent Psychiatry. **PANS is diagnosed when following an infection, a child who had previously been well has a sudden onset of obsessive-compulsive disorder (OCD), mood dysregulation, tics, food restriction behaviors, and a variety of other symptoms.** A similar syndrome called PANDAS (for pediatric acute onset neuropsychiatic disease associated with streptococcal infections) was first identified in children recovering from strep throat. The children suddenly developed OCD behaviors and tics after a streptococcal infection.

However, PANS is associated with a variety of infections, including viruses and other infections that do not involve streptococcus bacteria. PANS syndrome is typified by acute onset of obsessive compulsive disorder and food restrictions as well as two or more of the following symptoms: anxiety, mood swings and depression, irritability and aggression, behavioral regression, decreases in school performance, sensory motor abnormalities, and somatic alterations such as decreased sleep and urinary frequency, urgency, and/or incontinence. Tics are not part of the formal diagnosis, but are present in about 50% of patients.

In Chang's experience, the syndrome emerged 65% of the time in relationship to streptococcal infections, 13% with mycoplasma infections, 58% with viral infections, 39% in association with sinusitis, and 16% with otitis (inflammation of the ear). Increases in blood flow in the basal ganglia and increases in its volume likely occur due to antibodies that the immune system produces to fight infection, but which instead attack elements in the brain's striatum, including tubulin, calcium calmodulin kinase II, lyso-GM-1, and dopamine D1 and D2 receptors.

Chang suggested that a diagnostic workup for PANS should include: a complete blood count and screening for red blood cell sedimentation rate, mycoplasma antibodies IgG and IgM, anti-nuclear antibodies (ANA), ferritin (a protein that stores iron in blood), celiac disease, and other laboratory measures that are commercially available in a panel produced by the company Moleculera Labs. A more detailed description of the PANS syndrome and its diagnosis and workup is available in the most recent 2014 issue of the Journal of the American Academy of Child and Adolescent Psychiatry.

In a related poster, Jennifer Frankovich, another researcher in Chang's lab, reported that 62% of family members of children with PANS had a history of autoimmune disorders.

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Inflammation is Associated with Cognitive Dysfunction in Children with Bipolar Disorder

Researcher Ben Goldstein reported at the 2014 meeting of the American Academy of Child and Adolescent Psychiatry that children with bipolar disorder have levels of inflammatory markers in the same range as people with inflammatory illnesses, such as rheumatoid arthritis. In his research, **increases in the inflammatory marker c-reactive protein (CRP) occurred in proportion to the severity of manic symptoms in the children**.

Goldstein also discussed cognitive dysfunction, which is often seen early in the course of childhood onset bipolar disorder. Goldstein described studies showing that this type of cognitive dysfunction consists of a decrease in reversal learning, a measure of cognitive flexibility. Elevated CRP was significantly associated with deficits in a child's composite score for reversal learning.

Together these data suggest that inflammation could play a role in disease disability and cognitive dysfunction in childhood bipolar disorder.

Depression in Children with Inflammatory Bowel Disease

The incidence of irritable bowel disease has been increasing in recent years as obesity has increased. At a symposium at the 2014 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Eva Szigethy discussed depression in inflammatory bowel disease, which most often involves Crohn's disease or ulcerative colitis. These conditions are associated with increased levels of inflammatory markers such as interleukin 1 (IL-1), interleukin 6 (IL-6), and TNF alpha, and these in turn induce the acute phase reactive protein called c-reactive protein (CRP). The interleukins peak in the first 12 hours after an inflammatory challenge and CRP peaks at 48 hours and returns to normal at 120 hours. **Il-6 is most closely associated with the somatic symptoms of inflammation, including depression, fatigue, loss of appetite, and decreased sleep, while TNF alpha is associated with non-somatic symptoms, such as irritability.**

Szigethy found that in a randomized trial of cognitive behavior therapy versus supportive therapy in children with inflammatory bowel disease, inflammatory activity decreased significantly with cognitive behavioral therapy, and the therapy particularly helped the somatic symptoms of fatigue, sleep disorder, anhedonia (loss of interest in activities once enjoyed), appetite suppression, and mood dysregulation. In contrast, when antidepressants are given to those with inflammatory bowel disease, the drugs are not particularly helpful for these somatic symptoms. Inflammatory bowel diseases are treated with steroids in 21% of patients and with a genetically engineered drug called infliximab in 30%. Adding cognitive behavioral therapy to the regimen decreases CRP and red cell sedimentation rate, an associated measure of inflammation.

The discussant of the symposium on inflammation, Frank Lotrich, described how inflammation alters sleep, and this appeared to interact with genetic risk of illness. For example, those with certain genetic variations (the short SS allele of the serotonin transporter and the val-66-met allele of proBDNF) were most likely to experience sleep disturbance following treatment with interferon gamma, a treatment that fights the virus that causes Hepatitis C, creating inflammation in the process. Interferon gamma causes depression in about one-third of the patients who take it.

Lotrich pointed out that low levels of omega-3 fatty acids are associated with increased irritability and anger, and this is related to the presence of the A allele of TNF alpha. TNF alpha is also closely linked with irritability and anger, suggesting the possible benefits of omega-3 fatty acid supplementation to target irritability and anger more selectively. This would be consistent with the data of researcher Mary A. Fristad.

Il-6 is closely associated with the somatic symptoms of depression, particularly poor sleep, which is itself associated with increases in depression. This is consistent with inflammation being a marker of poor response to antidepressants; Lotrich noted that the selective serotonin reuptake inhibitors (SSRIs), which help depression, are far more effective against the non-somatic aspects of depression and less effective against low energy, decreased interest, and fatigue. However, extrapolating from the data on inflammatory bowel disease, cognitive behavioral therapy may be most helpful on these somatic symptoms.

Anti-Inflammatory Treatment Prevents the Effects of Stress in Female Rats

Women are more likely than men to experience depression, and this difference begins in adolescence, when girls show more sensitivity to stress. Researchers are studying how animals react to stress in the hopes of learning what mediates these gender differences in mental illness.

At a recent scientific meeting, researcher Jodi Lukkes and colleagues presented a study of stress and inflammation in female rats. The rats were exposed to different types of stressors. Some were separated from their mothers for four hours a day during the first 20 days of their lives. Later, some rats were exposed to an acute stressor, witnessing another rat receiving shocks. All the rats were placed in a box in which they could escape a shock by jumping to the other end of the box, in order to measure their motivation. Because drugs that inhibit the inflammatory enzyme COX-2 had reversed the effects of maternal separation in earlier studies, the researchers also treated some rats with these anti-inflammatories.

The researchers found that anti-inflammatory treatment could prevent behavioral consequences of stress in adolescent female rats. Witnessing another rat being shocked brought about deficits in motivation (a depression-like behavior), but **in rats that had received treatment with a COX-2 inhibitor, these deficits were reduced. The COX-2 treatment was only helpful to rats that had experienced an acute stressor in their lifetime, either maternal separation in infancy, or witnessing another rat receive the shocks.** A history of stress was required for the anti-inflammatories to improve motivation.

Lukkes and colleagues hope that this research begins to clarify the relationship between stress, inflammation, and gender. This may eventually lead to new targets in the treatment of depression.

Childhood Maltreatment Leads to Inflammation and Depression Later

Researcher Andrea Danese discussed the influence of childhood maltreatment on inflammation in a symposium at the 2014 meeting of the American Academy of Child and Adolescent Psychiatry. Danese indicated that inflammation is part of the normal immune system, which includes the blood brain barrier, recognition of self- versus non-self proteins, activation of cytokines and endothelial cells, and response by phagocytes and acute phase proteins. In an acute phase inflammatory response, the liver secretes proteins including c-reactive protein (CRP) and fibrinogen into the blood, where their levels can be measured.

Normal amounts of inflammation can be protective, while excessive or persistent inflammation can be damaging and pathological. The inflammatory cytokines interferon gamma and tumor necrosis factor (TNF alpha) induce an enzyme called indoleamine oxidase (IDO) that shunts the amino acid tryptophan away from its normal path, which yields serotonin, so that it instead yields kynurenine and then kynurenic acid, which inhibits the action of glutamate at NMDA receptors. Kynurenine can also be hydroxylated and turned into quinolinic acid, which activates glutamate NMDA receptors and causes toxicity.

In addition, inflammatory cytokines such as interleukin six (Il-6) can cross the blood brain barrier and directly influence neurotransmission. Meta-analyses have shown that inflammatory markers CRP, IL-6, IL-1, and IL-1 Ra all increase significantly in depression. A direct demonstration of the relationship between inflammation and depression is the finding that when hepatitis C is treated using the inflammatory treatment interferon gamma, there is about a 30% incidence of depression, which responds to the antidepressant paroxetine.

Stress can also increase the activity of the sympathetic nervous system, driving inflammation, and decrease parasympathetic activity, resulting in further inflammation. In addition, glucocorticoid receptor resistance can develop, enhancing depression, and increasing inflammation. Thus there are multiple ways inflammation can develop.

> Normal amounts of inflammation can be protective, while excessive or persistent inflammation can be damaging and pathological.

Danese described a study from New Zealand in which 1000 participants were observed over several decades—from childhood through age 38. The small percentage of **participants who experienced maltreatment as children (aged three to eleven) showed a linear increase in CRP in adulthood as a function of their histories of previous child maltreatment**. The maltreatment included parental rejection in 14%, sexual abuse in 12%, harsh discipline in 10%, changing caretakers in 6%, and physical abuse in 4%. Childhood maltreatment was also associated with some unfortunate outcomes in adulthood, including lower socioeconomic status, more major depression, more persistent depression, more cardiovascular risk, and more smoking. In other studies, Danese found that compared with controls, patients with depression alone, and patients with maltreatment alone, a greater number of patients with both depression and maltreatment (about 30%) had elevated CRP.

Danese noted that in a study by Ford et al. (2004), recurrent depressions, but not single depressions, were also significantly associated with increased CRP. In a meta-analysis by Nanni et al. in the *American Journal of Psychiatry* in 2012, Danese and colleagues found that across multiple studies, childhood maltreatment was associated with a twofold increase in the incidence of depression and a twofold increase in the persistence of depression (chronic depression or treatment resistance). The traditional optimal treatment for depression, combined psychotherapy and pharmacotherapy, was also significantly less effective in those with histories of childhood maltreatment. However, psychotherapy alone was equally effective in those with and without childhood maltreatment.

Together these data suggest that childhood maltreatment, partly through an inflammatory pathway, results in multiple difficulties in adulthood, including depression and treatment resistance. These data speak to the importance of attempting to prevent maltreatment in the first place, and ameliorating its consequences should it occur.

Editor's Note: In a 2014 article in the Journal of Nervous and Mental Disorders, *this editor Robert Post and colleagues reported that childhood adversity (verbal, physical, or sexual abuse) is associated with increases in medical comorbidities in adult patients with bipolar illness, and it is likely that inflammation could play a role in some of these medical conditions.*

Loving-Kindness Meditation Can Lengthen Telomeres in Women

Telomeres sit at the end of DNA strands and shorten with each cell replication. Shorter telomeres are associated with aging and an increase in multiple medical and psychiatric disorders, while some healthy behaviors including exercising, eating healthy, avoiding smoking, and even being married can help maintain telomere length. New data from researcher Elizabeth Hoge and colleagues suggests that a particular type of meditation can lengthen telomeres.

Previous research has found that three months of full-time meditation increased telomerase, an enzyme that repairs telomeres. **Loving-Kindness meditation, which comes from the Vipassana Buddhist tradition and focuses on positive intentions, unselfish kindess, and warmth towards all people, has been found to produce positive effects in individuals who practice it, including increasing positive emotions and sense of purpose, and bringing about improvement in physical symptoms including headaches, nasal congestion, and weakness.** Hoge and colleagues hypothesized that people who practice Loving-Kindness meditation would have longer telomeres than control participants of the same age, gender, education level, and experience of depression.

Participants who practiced Loving-Kindness meditation had been doing so near-daily for at least four years, and averaged 512 lifetime hours of this particular type of meditation, and 4,927 lifetime hours of any type of meditation.

The researchers found a trend toward longer relative telomere length in the Loving-Kindess meditation group compared to the control group, and significantly longer telomeres in women who meditated than in women who did not. The researchers conclude that meditation may have a positive effect on mortality.

Positive social habits that are focused on others, such as caring for a spouse, volunteering in the community, and practicing compassion, forgiveness, and altruism have been found to have health benefits. In a 2012 longitudinal study of elderly participants by Loren Toussaint et al. in the *Journal of Behavioral Medicine*, forgiveness was associated with longevity. Thaddeus W.W. Pace et al. reported in a 2009 article in Psychoneuroendocrinology that compassion meditation reduced levels of certain inflammatory markers.

Editor's Note: People with affective disorders or at risk for them should consider making some of these positive lifestyle practices part of their daily routine.

Childhood Adversity Associated With Shorter Telomeres

Telomeres are extensions of DNA strands that protect each chromosome during cell replication. Shorter telomeres are associated with aging and an increase in multiple medical and psychiatric disorders. New research draws connections between the production of mitochondrial DNA, telomere length, the experience of childhood adversity, and mental illness.

Researcher Audrey Tyrka and colleagues divided 290 healthy adults into four categories based on whether or not they had experienced adversity in childhood and whether they had been diagnosed with a mental illness in their lifetime, including depression, anxiety, and substance abuse. The researchers also analyzed the participants' telomere lengths and the copy number of their mitochondrial DNA. **Both stressful events in childhood (such as maltreatment or the loss of a parent) and a history of mental illnesses (depression and anxiety) were associated with shorter telomeres and higher mitochondrial DNA copy numbers, a measure of cellular aging.** Substance abuse was associated with higher mitochondrial DNA copy numbers.

Editor's Note: This research replicates earlier findings that adversity is associated with shortening telomeres. The finding that mitochondrial DNA could play a role in the long-term effects of early life adversity and mental illnesses is new.

Childhood Adversity, Gene Methylation, and Behavior Linked

Life experiences such as adversity in childhood have been linked to epigenetic changes to DNA. These changes do not affect the sequence of DNA, but can change how tightly DNA is wound, and thus how easily it is transcribed. **One epigenetic change that can occur following adversity in childhood is methylation of the gene for the glucocorticoid receptor (NR3C1).**

A recent study by Kathryn Ridout and colleagues examined links between early adversity, methylation of this gene, and behavioral problems in childhood. Adversity was linked to methylation of the gene at exons 1D and 1F in the promoter of NR3C1. Methylation of the gene was associated with internalizing behaviors (e.g. depression, anxiety) but not externalizing behaviors (e.g. attention deficit hyperactivity disorder (ADHD) or oppositional defiant disorder) in children of preschool age. The NR3C1 methylation was a significant mediator of the internalizing behaviors in children who had experienced adversity.

Editor's Note: Similar associations of methylation of the glucocorticoid receptor with childhood adversity have been reported in other clinical and animal studies and provide a mechanism for the long-lasting adverse effects of stressors in childhood.

Maternal Anxiety Affects Information Filtering in the Infant Brain

Sensory gating is a process by which the brain filters out unimportant information, to avoid flooding higher cortical centers with irrelevant stimuli. New research from Randal Ross and colleagues shows that infants of mothers with anxiety have deficits in the way their brains inhibit response to this type of irrelevant information.

Mothers who were rated higher on the trait of anxiety had paradoxically lower levels of the inflammatory cytokine interleukin 6 at week 16 of their pregnancy, and had one-month-old infants who showed deficits in sensory gating. The reasons for these relationships requires further investigation.

Choline is a nutrient found in liver, muscle meats, fish, nuts, and eggs, and it may help. In a 2013 article in the *American Journal of Psychiatry*, Ross and colleagues showed that the supplement phosphatidylcholine (which converts to choline), taken during the second and third trimesters of pregnancy (at doses of 6300 mg/day, the equivalent of about three eggs) and followed up with 700 mg/day in the infant, led to improvements in sensory gating in the infants. These infants went on to have fewer behavioral problems as toddlers.

Ross and colleagues suggest that pre- and post-natal choline supplementation may be able to reverse the effects of maternal anxiety on infants. The researchers believe it could be helpful in the prevention of schizophrenia, as insufficient cerebral inhibition (decreased sensory gating) is a characteristic of that illness as well.

Maternal Childhood Adversity Associated with Low Infant Birth Weight

In a study of the effect on infant health of a mother's experience of adversity in childhood by researcher Deborah Kim and colleagues, both adversity in childhood (such as physical abuse or the loss of a parent) and stress during pregnancy were associated with low infant birth weight and lower gestational age at birth.

Among 146 women enrolled in the study, 58.2% percent scored a 0 on the Adverse Childhood Experience Questionnaire (ACE), 24% scored a 1, and 17.8% scored a 2. Those who scored higher on the ACE also scored higher on a scale measuring perceived stress. A score of 2 or higher on the ACE was associated with lower gestational age at birth, indicating infants born prematurely. **Greater stress during pregnancy was also associated with lower gestational age at birth and lower infant birth weight.** When potential confounding demographic factors were removed from the analyses, ACE scores of 2 or higher were still associated with lower infant birth weight, while perceived stress was no longer associated with either low birth weight or gestational age.

Childhood adversity is associated with increases in inflammation and multiple adverse medical consequences in adults. The researchers called childhood adversity a "significant predictor of poor delivery outcomes" for women.

Editor's Note: This research shows that a mother's health and earlier life stressors could have an adverse effect on her child.

Childhood adversity leaves behind a residue of neuroendocrine and neurochemical alterations that can persist into adulthood. Many are mediated by epigenetic changes, consisting of small chemical marks that attach to DNA and the histones around which it is wrapped.

In addition to these neurobiological alterations mediated by epigenetic effects, there is new evidence that some epigenetic marks can be passed on to the next generation via a mother's egg or a father's sperm. Thus, either directly or indirectly, parents' adverse life experiences can influence the health of their offspring.

Early Life Stressors Lead to Lifetime Increase in Inflammation in Mice

Stressors in early life can contribute to the risk of developing mood disorders. Given that many treatments for mood disorders work by blocking the serotonin 5-HT transporter, Nicole Baganz and colleagues designed a study to see whether an early life stressor, in this case maternal separation, would affect immune processes that in turn affect serotonin signaling.

In this study as in many before it, mice that were removed from their mothers exhibited behaviors that resembled human anxiety and depression. They were also found to have elevated messenger RNA for several inflammatory cytokines (including IL-1beta and IL-6) in their brain and blood. Mice that had a gene for the interleukin-1 receptor (IL-1R) removed exhibited neither the depressive behavioral effects nor the changes in cytokine levels following maternal separation, showing that the IL-1R gene plays a necessary role in the signaling process that leads to this type of depression. Levels of the stress hormone corticosterone in the blood did not differ in the mice with and without the IL-1R gene.

The researchers concluded that early life stressors can cause lifelong changes in inflammatory cytokine levels in mice.

Young Rats That Witness Maternal Abuse Show Depression-Like Behavior in Adulthood

Rodents that are subjected to social defeat (being overpowered by a bigger, more aggressive animal) develop a syndrome that resembles human depression—they avoid social interaction, lose interest in sucrose, and do less exploring of new places or other animals. A recent finding showed that even witnessing the social defeat of a peer was enough to bring about the depressive behaviors. The same researchers, led by Samina Salim, recently found that **young rats (aged 21–27 days) that witnessed their mother go through the trauma of social defeat showed depression-like behavior themselves as adults (at age 60 days)**.

The rats saw their mothers defeated by the larger rat every day for seven days. As adults, those who witnessed this abuse exhibited depression-like behavior compared to rats of the same age and gender that had not witnessed abuse. The depressive rats gave up more quickly on a test of forced swimming. Male rats showed great depression-like behavior than female rats.

It has been estimated by the American Psychological Association that 15.5 million children in the US witness physical or emotional abuse of a parent (usually their mother). Children who witness domestic violence often show symptoms of post-traumatic stress disorder (PTSD). This rodent research may lead to a better understanding of the consequences of witnessing trauma in childhood, and potential treatments that could help.

Editor's Note: These data show that rats have something like empathy, and that the psychological aspects of stress (including verbal abuse in humans and witnessing another's abuse in rodents) may have profound and lasting consequences on behavior.

Heart Attacks Lead to Memory Impairment in Mice

Events like surgery or heart attacks that cause inflammation can lead to cognitive deficits or depression for months or years afterward, even though the direct effects of inflammation wear off within weeks. In a recent study, Natalie Tronson and colleagues subjected mice to surgical heart attack, sham surgery, or no operation, and observed how well they absorbed new learning eight weeks later.

Both male and female mice had impairments in fear learning following surgical heart attacks. Female mice that received sham surgery also showed deficits in fear learning. When the researchers dissected the mice, analyzing their blood and hippocampi after the eight-week period, inflammatory cytokine measures had normalized as expected, but the researchers found other abnormalities.

Intracellular signaling was dysregulated, and there had been epigenetic changes in cells of the hippocampus. (Epigenetic changes refer to those that change the structure of DNA, such as how tightly it is wound, rather than its sequence. For example, the addition of acetyl groups to DNA or the histones around which it is wound.) The researchers observed increased histone acetylation and phosphoacetylation following the heart attacks.

The researchers concluded that **a systemic inflammatory event, such as heart attack or surgery, can cause long-term memory impairment and changes in mood through epigenetic mechanisms.** They compared the findings to those of other studies in which normal aging and memory-impairing treatments such as chemotherapy had also been associated with increases in histone acetylation or decreases in histone deacetylase activity.

Output From the Amygdala Mediates Reward or Fear Memories

People and animals can rapidly learn to associate environmental stimuli with positive or negative outcomes, learning what to approach or avoid as they go through daily life. The amygdala plays a role in this type of emotional learning, which can be disrupted by mood disorders. In new research, Praneeth Namburi and colleagues determined that activity at the synapses in the basolateral amygdala reveals differences in the creation of fear memories and reward memories.

In animals trained with reward and fear conditioning tasks, photostimulation of neurons that then travel from the basolateral amygdala complex to the nucleus accumbens (the brain's reward center) is positively reinforcing, while photostimulation of neurons that will travel from the basolateral amygdala complex to the centromedial nucleus of the amygdala causes aversion. There are genetic differences between the two types of neurons, including a difference in the gene for the neurotensin-1 receptor. The researchers found that neurotensin, a neuropeptide, modulates glutamate's effect on neurons, causing some to project to the nucleus accumbens and some to project to the centromedial nucleus of the amygdala.

The researchers wrote that the results "provide a mechanistic explanation, on both a synaptic and circuit level, for how positive and negative associations can be rapidly formed, represented, and expressed within the amygdala."

Editor's Note: The amygdala's creation of opposing outputs may provide clues to the mechanisms behind mania (involving the nucleus accumbens) and depression (involving the centromedial nucleus of the amygdala).

Opiate and Alcohol Abuse

Deaths from opiate abuse are occurring in the US at about the same rate as automobile fatalities. At a recent talk, researcher Richard Ries discussed treatment of opiate addictions and the current epidemic of unintended opiate overdoses. Most opiates being abused come from other people's leftover prescriptions. The best way to prevent opiate abuse is to throw out unused painkillers when they are no longer needed.

Many overdoses from opiates also involve alcohol and benzodiazepines, which can contribute to breathing difficulties.

There are several treatments available that can help patients abstain from using opiates. Treatment with opioid receptor antagonists (such as naltrexone (Rivia or long-acting Vivitrol, which is taken as an injection and lasts for 1 month), partial agonists (like buprenorphine), or full agonists (like methadone) results in, on average, an 80% decrease in the rate of hospitalization and an 80% reduction in crime, as well as a marked decrease in AIDS transmission. Without treatment, it is very difficult for people with opiate addictions to maintain abstinence, and relapse rates are extraordinarily high.

Treating Alcohol Abuse, Avoiding Benzodiazepines

Ries also discussed data on treatment of alcohol abuse. He emphasizes that some aspects of withdrawal, such as sleep disturbance, can last a month or more after a parient's last drink, putting the patient at high risk for relapse. Gabapentin, which is most often prescribed to prevent seizures, helps patients with this phase. Ries endorsed the combination of gabapentin and naltrexone as especially helpful. Carbamazepine is widely used in Europe for the treatment of alcohol abuse, and Ries also strongly endorsed the drug as another way of avoiding benzodiazepines. Several large placebo-controlled trials suggest that the anticonvulsant topiramate is also effective for long-term alcohol avoidance.

Editor's Note: Another researcher, Mark Frye, found that women with bipolar disorder are almost seven times more likely than women in the general population to abuse alcohol, often in an attempt to self medicate their residual anxiety and depression. Excellent treatment of mood in bipolar disorder may have the double benefit of helping patients avoid alcohol abuse. The nutritional supplement n-acetylcysteine (NAC) also helps improve mood in bipolar disorder and has positive placebo-controlled data in heroin, cocaine, and alcohol avoidance.

NAC Reduces Cutting Behaviors

Cutting, or non-suicidal self injury, is a serious problem among adolescents, and few treatments are available. Researcher Kathryn Cullen and colleagues have found that N-acetylcysteine (NAC), an antioxidant nutritional supplement that has been effective in the treatment of depression and many addictions and habit-related behaviors, can reduce cutting.

The study included 25 participants with a history of non-suicidal self injury, aged 13–21, and 12 controls. They participated in brain scans before and after treatment. Compared to the controls, the self-injurers showed greater overall psychopathology, greater activation in a few brain regions (precuneus, posterior cingulate, insula, and temporal lobes), and reduced lower left frontal activation. **Patients who received NAC up to 900mg twice daily in weeks 5–8 of the study reduced their cutting and also showed reduced psychopathology.** An increase in frontal activation in response to negative emotion was linked to the reduction in cutting.

Editor's Note: NAC improves mood in depression, many addictions, and many habits including trichotillomania (excessive hair-pulling), nail biting, and cutting. It may do this by increasing glial glutamate transporters in the nucleus accumbens, the brain's reward center, which lessens the magnitude of the glutamate signal, mediating the compulsion to engage in the habitual behavior.

The Combination of N-Acetylcysteine and Varenicline Reduces Nicotine Addiction in Rats

Nicotine addiction is highly cue-dependent, meaning that certain situations or places will make smokers crave a cigarette even if they're trying to quit. Researchers working with rodents are exploring a combination of treatments that address different behavioral and neurobiological mechanisms to reduce nicotine addiction. In a recent study by Cassandra Gipson-Reichardt and colleagues, **N-acetylcysteine reduced cue-induced nicotine seeking, while varenicline reduced nicotine self-administration. Together the drugs worked better to reduce nicotine relapse than either drug on its own.**

In the study, rats were trained to self-administer nicotine (with 0.02mg/kg infusions), and cues were used to reinstate nicotine seeking. The rats were treated with 10 and 30 mg/kg injections of NAC and 1 and 3 mg/kg injections of varenicline.

Relapse is associated with rapid synaptic potentiation in the reward area of the brain, the nucleus accumbens. In addition to the positive behavioral changes noted, NAC also inhibited this synaptic potentiation, limiting rapid changes in the size of spines on dendrites and reducing the ratio of AMPA to NMDA (two different compounds that mimic glutamate) in the core of the nucleus accumbens.

Editor's Note: The combination of NAC and varenicline has not yet been studied in humans, but because both compounds are effective in reducing smoking, it is likely that this animal research on nicotine will be replicated in humans who are addicted to the nicotine in cigarettes.

In Studies of Mice, White Blood Cells Convey Resilience to Stress

Mice subjected to chronic defeat stress (being placed in the home cage of a larger, more aggressive mouse) behave in ways that resemble human anxiety and depression. In new research by Miles Herkenham and colleagues at the National Institute of Mental Health designed to explore the adaptive immune system's affect on mood, mice exposed to this type of stress showed increases in inflammatory cytokines in the blood (including TNFalpha, IL-1beta, IL-2, IL-3, IL-6, IL-17, and IFNgamma) compared to a control group. Interestingly, when white blood cells (lymphocytes) from stressed animals were transferred to a new set of animals, the recipient mice seemed to benefit from greater resilience to stress in a variety of ways.

Mice that received white blood cells from defeat-stressed animals had lower levels of TNFalpha, IL-1beta, IL-2, IL-3, and IL-17 than a control group that received white blood cells from unstressed mice. The recipient mice also exhibited reduced anxious and depressive behaviors in a litany of behavioral tests compared to both the group that received white blood cells from unstressed mice and a group that received a saline injection instead. Lastly, the recipients of the white blood cells from stressed animals showed more new neurons in the dentate gyrus of the hippocampus. (Hippocampal neurogenesis is decreased by stressors and increased by antidepressants.)

Herkenham and colleagues concluded that psychopathology is not just a downward spiral—the immune system plays an active role in adapting to stress, with lymphocytes being programmed by stress to provide antidepressant functions.

Editor's Note: These data add a new twist to the studies of Scott Russo, who found that IL-6 secreted by white cells of animals subject to defeat stress was the cause of the depressive-like behaviors they exhibited. If IL-6 was blocked, the behaviors did not occur. Now it would appear from Herkenham's work that something about the timing, the type of cytokines, or the transfer of the white cells conveyed protective antidepressant-like effects in this case.

Oxytocin Can Block Stress-Induced Relapse of Cocaine Seeking in Animals

Stress can trigger former drug users to begin taking drugs again. In clinical trials, the bonding hormone oxytocin has been found to reduce stress-induced cravings for certain drugs, including alcohol and marijuana. A new study in animals suggests that oxytocin may be able to reduce stress-induced cocaine cravings as well.

Brandon Bentzley and colleagues combined an unpredictable shock to the foot with an alkaloid called yohimbe that comes from a particular tree bark to apply stress to animals who had previously developed a cocaine self-administration habit that had since been extinguished. **The combination of the foot shocks and the yohimbe brought back robust reinstatement of the animals' cocaine seeking behaviors, but pretreatment with oxytocin (at doses of 1 mg/kg) prevented this reinstatement.**

This research suggests that oxytocin has potential to prevent stress-induced cocaine cravings in people.

Connections Between Stress and Substance Use May Be Mediated By Hormone CRF

Researchers hope to map out the neurocircuitry by which stress leads to compulsive drug taking. A recent study by Klaus Miczek and colleagues examined different rodents' responses to the stress of being repeatedly placed in the cage of a larger, more aggressive rodent, developing what is known as defeat stress, a set of behaviors that mimic human depression. **Mice and rats showed increases in the stress hormone corticosterone that did not diminish over repeated run-ins with a larger animal. Rodents who were exposed to this stress became sensitized to cocaine or amphetamine, showing hyperactivity that increased each time they accessed the drug (the opposite of a tolerance response).** Some also "binged" on cocaine, which they were able to self-administrate by pushing a lever to receive infusions. The mice and rats that went through the social defeat showed elevated levels of dopamine in the nucleus accumbens, the brain's reward center. Levels were related to the severity of their stressful experience.

Later the rodents had a choice between water and a 20% alcohol solution. The researchers determined what type of stress led the rodents to consume the alcohol solution instead of the water. The maximal effect was seen in two types of mice that suffered an attack of less than five minutes that resulted in a moderate number of attack bites (30); this resulted in the mice consuming large amounts (15–30 g/kg/day) of the alcohol solution. Earlier sensitization to cocaine or amphetamine did not predict later alcohol or cocaine self-administration.

When the researchers injected the rodents with antagonists of the receptors for corticotropin-releasing factor, a hormone and neurotransmitter important in stress response, prior to each episode of social defeat, the rodents did not escalate their cocaine or alcohol self-administration, indicating that CRF plays an essential role in the process by which stress makes animals prone to using substances.

ADHD and Bipolar Disorder Are Inherited Separately

While attention-deficit hyperactivity disorder (ADHD) is fairly common among people with bipolar disorder, the genetic risks of inheriting these two illnesses run separately in families. In a recent study of 465 people and 563 of their first-degree relatives by Susan Shur-Fen Gau and colleagues, **people with bipolar I disorder were likely to have relatives with bipolar I disorder, and people with ADHD were likely to have relatives with ADHD, but ADHD did not increase risk of bipolar disorder and vice versa.**

The researchers hypothesize that other reasons people might develop both disorders include developmental precursors to the illnesses, neurocognitive functioning, sleep problems, and personality traits such as impulsivity and disinhibition.

Editor's Note: At a recent scientific meeting, Gau and her colleague Kathleen Merikangas said that people with bipolar disorder in the study were five times more likely to have relatives with bipolar disorder. Bipolar disorder and ADHD were comorbid in 37.8% of those with bipolar I disorder, 16.4% in bipolar II disorder, 14% in depression, and 1.1% in normal controls.

Typically, the very high comorbidity of bipolar disorder and ADHD that is present in childhood decreases substantially in adolescence, and even further in adulthood.

RTMS Can Increase Amygdala Connectivity

Regulation of the amygdala (the brain's emotional center), particularly through its interaction with the ventral anterior cingulate cortex, has been implicated in the experience of fear in animals, and anxiety and depression in humans. Connectivity between the two structures is critical for emotion modulation. Repeated transcranial magnetic stimulation (rTMS) is a method of stimulating outer regions of the brain with magnets. Researchers Desmond Oathes and Amit Etkin are investigating whether rTMS can also be used to influence these deeper brain areas, or their interaction with each other.

The researchers' study used single-pulse probe TMS delivered at a rate of 0.4 Hz at 120% of each participant's motor threshold, targeted at the anterior or posterior medial frontal gyrus on either side of the brain. The researchers also used functional magnetic resonance imaging (fMRI) of the whole brain to observe connectivity between different sections.

RTMS to the right side of the medial frontal gyrus increased connectivity between the amygdala and the ventral anterior cingulate cortex more than stimulation to the left side. Stimulation of the posterior portion of the medial frontal gyrus increased connectivity more than stimulation of the anterior portion.

Editor's Note: These data indicate that rTMS can alter brain activity in these deeper regions and can influence inter-regional connectivity. This is important because abnormalities in the connectivity of brain regions have increasingly been found in patients with mood disorders. Oathes and Etkin hope that these findings can be applied to others and that rTMS can be used to correct patterns of regional connectivity in the brain in order to improve emotion regulation.

Lavender Oil Has Anti-Anxiety Effects and Possibly Antidepressant Effects

An oral preparation of lavender oil called Silexan was previously found to reduce anxiety in people with generalized anxiety disorders or subthreshold anxiety symptoms without causing sedation. It seems to work by inhibiting voltage dependent calcium channels in a manner similar to the anti-anxiety drug pregabalin. Unlike pregabalin, the lavender oil treatment also reduced depression in the people with subthreshold anxiety. Researchers, led by Walter Mueller, are now exploring lavender oil's effects on rats who exhibit behaviors that resemble human depression, and on rat and human cells in vitro.

Silexan had positive effects on rats with depression-like behaviors, increasing the time they would swim before giving up in a forced swim test. It also increased the growth of rat and human neurons in a lab setting.

These effects are usually connected with activation of a protein called CREB that turns on some genes that affect mood. The researchers were able to clarify the pathway for this activation by inhibiting specific kinases, enzymes responsible for transferring phosphates across different molecules. The kinases involved included PKA, PI3K, MAPK and CaMK IV.

Editor's Note: It remains to be seen wehther oral lavender supplements may be a non-sedating way to improve anxiety and depression.

To Investigators or Clinicians in Bipolar Disorder,

We are reaching out to you to let you know about a new study that the Bipolar Collaborative Network is implementing called the Child Network. Our goal is to **foster collective knowledge about childhood bipolar and other disorders by acquiring data about children who have or may be vulnerable to childhood-onset mood and bipolar disorders and associated conditions**. Depressive, oppositional, and bipolar disorders as well as anxiety in very young children have not been well studied for their course and for treatment effectiveness and tolerability. Our goal is to compile and analyze the varied treatments for children with these disorders. How well a child responds to a specific treatment may provide new preliminary information of use to others, and assist parents and physicians in assessing treatment options.

The Child Network is specifically for parents of children ages 2 to 12 who have few symptoms, minor (prodromal) symptoms, or the full onset of their illness, including bipolar disorder, prior to age 13. We also seek parents who have been diagnosed with a bipolar disorder to rate their own children who are genetically at higher risk for a mood disorder but as yet display no symptoms. A small percent of these children may eventually develop an anxiety, depressive, or bipolar disorder in childhood. It is estimated from several studies that more than ¼ of adults in the United States with a confirmed diagnosis of bipolar disorder experienced a very early onset in childhood (before age 13). However, many of these individuals did not receive treatment for their illness for 10-15 years following initial onset of the illness, and this delay was associated with a more difficult course of illness.

Participating in the Child Network will primarily involve a weekly ten-minute parental assessment of their child, as well as confidential disclosure of medications and other treatments and any side effects that occur in the prior week. There will also be a short demographics questionnaire and a once a year more detailed symptom checklist. This study does not involve treatment. The network is only meant to document what is currently being done in the community. The child of participating parents will continue to be treated according the child's physician's preferences. Studies in this network will not involve randomized or controlled clinical trials or use of placebo, but rather will examine what agents and their combinations that children are already taking are effective, and for which children.

We believe that this network will also benefit its participants. Parents will be able to print out results of the ongoing brief weekly ratings in a graphic form so that the course of the child's symptoms can easily be visualized. Also, although family members already have access to general information provided in the Bipolar Network News (BNN), participation in this study may help attune parents to the complexities of treatment and engender more careful reading of the BNN and other literature.

We hope that this brief description of the Child Network study helps to orient you to its purpose and that your organization will pass on our introductory remarks to your members. We also encourage you and parents to visit www.bipolarnews.org and click on the tab for Child Network to learn more about the Child Network and to access the informed consent documents.

Thank you for your time.

Robert M. Post, MD and Michael Rowe, PhD
Bipolar Collaborative Network , and
Robert L. Findling, MD, MBA, Principal Investigator

This research study is IRB approved by the Johns Hopkins University School of Medicine
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