REVIEW ARTICLE

The inflammation hypothesis and mental illness

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Contemporary neuroscience and psychiatry are currently experiencing a rapid evolution. The foundations of these relatively new sciences are still largely theoretical and speculative. There are many competing hypotheses regarding the etiology and pathogenesis of mental illness. Unlike most somatic pathology, there is not a single laboratory test or objective disease marker for any psychiatric disorders. One of the dominant etiological paradigms in psychiatry involves the functional levels of neurotransmitters. Even this assumption is mootable, untestable, and widely disputed.

Several psychiatric disorders - Depression, Schizophrenia, Bipolar Disorder, Alzheimer's disease, Traumatic Brian Injury, Autism, Parkinson's disease, and Post-Traumatic Stress Disorder are associated with a dysregulation of immune responses and measurably increased inflammatory markers.

There is an empirical correlation of an over-activated immune system with the development of psychiatric symptomatology. By experimentally inducing systemic inflammation, cognition and behavior are adversely affected. By experimentally suppressing inflammation, sensorium and mood can be dramatically improved.

Anti-inflammatory agents such as NSAIDS (COX-2 inhibitors), low-dose Aspirin (COX-1 inhibitors), and Polyunsaturated Fatty Acids (Omega-3 Fatty Acids) have demonstrated effectiveness – sometimes surpassing first-line psychotropic medications – in reducing psychiatric symptomatology.

It has also been demonstrated that some antidepressant and antipsychotic medications exert measurable immune modulation and anti-inflammatory effects. This may in part explain some of their therapeutic actions further challenging the theoretical foundation of the neurotransmitter hypothesis.

The notion of neuroinflammation is opening the door to a groundbreaking scientific endeavor. There is even a debate among these trailblazing scientists about what to call this promising and emerging field; Immunopsychiatry or Psychoneuroimmunology.

A conspicuous question is then raised as to whether inflammation causes mental impairment or does psychiatric pathology induce inflammation? Is inflammation the chicken or the egg? This is an exciting new frontier in psychiatry. It will offer promising novel targets for treatment and new avenues for therapeutic innovation.

Key Words: *Inflammation; Hypothesis; Cytokine; Immunity; Microbiome; Probiotic*

INTRODUCTION

Empirical evidence

Inflammatory biomarkers: Over the past twenty years, numerous investigations have identified elevated biomarkers for inflammation in patients suffering from major depressive disorder, schizophrenia, and bipolar disorder [1,2]. The abnormal levels of these inflammatory molecules, called cytokines, suggest a correlation between psychiatric symptoms and inflammation. A "cytokine hypothesis" has been speculated suggesting that inflammation aroused by either internal or external stressors could trigger depression [3].

It is well known that children who have experienced childhood abuse or neglect are more likely to develop psychiatric symptomatology in adulthood. Similarly childhood adversity is also associated with amplified levels of inflammatory mediators further validating a relationship between inflammation and mental illness [4]. There are significantly elevated levels of C-reactive protein and cytokines IL-6 and TNF-α in adults exposed to childhood adversity [5].

Generalized inflammation results in a cluster of symptoms that are often associated with psychological depression. These symptoms include lack of energy, sleep disturbances, appetite changes, lethargy, anhedonia, depressed mood, low self-worth, impaired concentration, and suicidal ideation. These reactions are referred to as "sickness behaviors" [6].

Elevated levels of the inflammatory messenger, C-reactive protein, are often found in patients suffering from depression [7]. An over-activated immune system appears to be correlated with depression. This suggests, in part, a physiological basis for depression.

During the 12 year follow-up of the large Nurses' Health Study, involving over 43,000 participants, the risk of depression was increased in nurses who had higher inflammatory mediators [8]. In addition, dietary patterns that are known to be pro-inflammatory also resulted in depressive symptoms. These findings seem to indicate that chronic inflammation is a possible link between diet and depression.

An investigation searching for a diagnostic blood test for major depressive disorder was published in Molecular Psychiatry in 2013 [9]. The researchers evaluated serum levels of nine different biomarkers of inflammation. With reliable sensitivity and specificity, the investigators were able to distinguish patients suffering from depression from non-depressed individuals on the basis of these objective lab findings. Subjects with elevated levels of immune makers were more likely to be depressed.

Elevated inflammatory biomarkers may even be a proxy for treatment resistant depression. High levels of C-reactive protein have been identified in patients that have failed to respond to antidepressant medications [10]. These markers can possibly be used to predict response to antidepressants.

Post-traumatic stress disorder has also been investigated in an attempt to identify markers of inflammation. A study published in Lancet Psychiatry revealed that people suffering from PTSD had increased levels of immune molecules in their blood [11]. The authors even suggested that low-grade inflammation could be a potential new target for the pharmacological adjunctive treatment of PTSD.

In teenage victims of suicide, inflammatory biomarkers were also identified. The researchers found significantly increased inflammatory mediators on autopsy in the prefrontal cortex of teens who died of suicide [12]. These results might suggest a possible predictive test for suicide risk. The authors even propose targeting inflammation in the development of new medications for suicide prevention.

An even more recent meta-analysis investigated postmortem brain samples, cerebrospinal fluid, and serum of patients with completed suicides or

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suicidality. The researchers identified higher levels of inflammatory markers in patients with high suicide risk compared to non-suicidal healthy controls. The authors concluded that the cytokines, IL-1β and IL-6, could predictably distinguish suicidal patients from non-suicidal controls [13].

Suicides and self-directed violence have been shown to increase when grass, ragweed, and tree pollen levels are elevated. The seasonal pattern of suicide and para-suicidal behavior is likely due to elevated pollen counts [14]. The mechanism that is proposed to account for this finding is increased inflammatory activation in response to airborne pollen.

A relationship between aggressive behavior and inflammation was revealed in an investigation of inpatients suffering from schizophrenia. Elevated levels of the inflammatory marker, C-reactive protein, were associated with increased aggressiveness compared to inpatients with normal levels of this biomarker [15]. The chance of being physically restrained during hospitalization was 2.5 times greater for patients with elevated C-reactive protein compared to patients with normal levels. This suggests a possible a biological correlate for aggression and potential target for treatment.

In patients suffering from schizophrenia, increased inflammatory markers such as TNF-α and IL-12p70 were associated with poorer daily functioning and increased neurocognitive impairment [16]. Patients who are a high risk for psychosis and schizophrenia have measurable increases in inflammatory microglial activity [17]. The severity of symptoms corresponds to the magnitude of the immune response indicating neuroinflammation as a risk factor of psychosis and expression of symptoms. This might suggest that anti-inflammatory treatments might have a role in the prevention of psychosis or its amelioration.

Infections and autoimmunity: The evidence from this and other recent research is tilting in favor of the "inflammation & neurodegenerative hypothesis" as a crucial contributing factor in the development of psychopathology [3].

In Denmark, a groundbreaking investigation into the risk factors for mood disorders was published in 2013 [18]. A nationwide survey examined the medical histories of over 3.5 million citizens over a 50 year period. This study focused on the pathophysiological mechanisms that might prove to be predictive for mood disorders.

The researchers discovered that people who had been hospitalized for a prior infection had a 62 percent increased risk of developing depression or bipolar disorder. The Danish investigation also revealed that people who were diagnosed with autoimmune disorders had a 45 percent increased chance of developing a mood disorder [18]. Furthermore, a "dose-response" relationship was found whereby the number of infections or autoimmune diseases directly increased the incidence of mood disorders.

In a similar national cohort study, the risk of developing schizophrenia was revealed to have a significant dose-response relationship to past exposure to infections and autoimmune diseases [19]. A medical history of autoimmunity or infections requiring hospitalization is a risk factor for the development of schizophrenia.

A follow up investigation examined the relationship between individuals hospitalized for an infection and the subsequent risk of death by suicide. A large sample size involving over 7 million adults in Denmark during a 32 year period revealed a predictive correlation of infections on the occurrence of death by suicide. There was a dose-response effect whereby the number of days required for the treatment of infections corresponded to directly to an increased risk of suicide [20].

In a cohort study of the entire population of Sweden, a similar conflation was discovered. In an effort to uncover comorbidities of psychiatric disorders with inflammatory conditions, the study examined psychosis, affective conditions, personality disorders, neurosis, delirium, and dementia [21].

The researchers discovered that Swedish citizens with inflammatory conditions had an increased risk of requiring psychiatric hospitalization compared to the general population. A corresponding relationship was also revealed whereby individuals who had psychiatric diagnoses were more likely to suffer from inflammatory conditions.

These discoveries fortify the theory of a common network involved in the pathophysiology of immune disorders and psychiatric pathology. One author even questioned whether depression was, in fact, a type of allergic reaction [22]. Depression can be experimentally induced by activating the immune system [23]. Using vaccines that arouse inflammation, injecting various cytokines, or administering immunologic irritants, the symptoms of mood disorders can be artificially induced.

Some cancer drugs, antiviral agents such as interferon, and other caustic medical treatments can result in increased inflammation. These drugs are well known for causing depression and producing neurovegetative side effects such as fatigue, appetite disturbance, psychomotor retardation, and sleep problems [4].

At the same time, experimentally induced depression has been shown to result in increased serum levels of inflammation molecules. After establishing a baseline of immune markers, a group of experimenters instructed volunteers to focus on a past experience of profound sadness for 45 minutes [24]. By evoking sad feelings, the test subjects produced significantly elevated levels of inflammatory chemicals in their circulation. This effect was even greater in volunteers that were already suffering from depression.

Anti-inflammatory medications: One of the surprising pharmacological properties of antidepressant medications, particularly SSRIs, some antipsychotic drugs, and a few mood stabilizing agents is that they have intrinsic anti-inflammatory properties. The immune suppressive action of these drugs might even explain some of their therapeutic action. This challenges the long held theory of neurotransmitter depletion in depression [2].

Anti-inflammatory drugs have been demonstrated to be effective adjuncts in reducing psychiatric symptomatology [25]. Although the effect sizes are small, NSAIDs have shown promise in treating schizophrenia, including negative symptoms and cognitive functions, as well as being effective adjuncts for treating bipolar disorder.

Acetaminophen, ibuprofen, and low-dose aspirin (acetylsalicylic acid) have also been demonstrated to be moderate but useful augmenting agents in the treatment of major depressive disorder and schizophrenia [25,26].

In addition, individuals who take NSAIDs regularly have a reduced risk of developing Alzheimer's disease later in life [27]. The anti-inflammatory effects of NSAIDs seem to interfere with the accumulation of amyloid plaque in the brain.

Brain lymphatics: Until recently it was presumed that the brain was "immunologically privileged" and unaffected by immune responses in the rest of the body. The central nervous system was believed to be isolated. It was only recently that a previously unknown anatomical structure in the human brain was discovered by researchers [28].

A series of channels in the brain were revealed that are composed of lymphatic tissue and glial cells. These vessels function by circulating cerebrospinal fluid and white blood cells in the brain while removing metabolic waste products and dead cells as well as isolating toxins.

The implications of this newly discovered lymphatic system in the brain – referred to as the "glymphatic system" – are dramatic and far-reaching. This groundbreaking discovery identifies a physical or anatomical structure that in part accounts for the mind-body connection.

In just the last several years, an autoimmune disorder marked by antibodies attacking specific receptors in the brain was discovered. Antibodies targeting NMDA receptors in the brain can result in psychosis and paranoia. This newly discovered syndrome manifests in behavioral changes like aggression, cognitive and memory deficits, mutism, and aphasia which can easily be mistaken for a psychiatric disorder.

The discovery of Anti-NMDA Receptor Encephalitis raises the question whether other psychiatric disorders and psychoses might be caused in part by a self-destructive allergic reaction or unchecked autoimmune response [29]. It is suggested that these antibodies are initially produced in reaction to a tumor. The antigenic profile of this neoplastic tissue is similar to some

brain cells. The antibodies produced in response to the tumor cross-react with NMDA receptors thereby attacking an individual's own synapses.

Invading microbes: Psychiatric symptoms that are produced by an activated immune system are hardly a new observation. Immediately following the influenza epidemic of the 19th century, physicians documented an outbreak of depression [6]. This suggested some yet-to-be discovered role of infection in the causality of mental illness.

In the early 20th century, mental illness was believed to be curable when neurosyphilis resulting in erratic behavior was successfully remedied with penicillin [29]. There was great enthusiasm that infectious agents might account for insanity and these could be identified and treated.

Acute infections and prolonged fevers were observed to produce "sickness behavior" in animals. Signs of depression such as lethargy, loss of appetite, sleep disturbances, alterations in grooming behavior, and disrupted social interactions were described by veterinarian Benjamin Hart in the 1980's [6].

Even now some experts are questioning whether the inflamed state that coincides with depression might be caused by an invading microbe. It has been suggested that some psychiatric disorders are actually infections [30]. Pathogens such as bacteria, fungi, viruses, or parasites can cause an over-activation of the immune system.

A number of neuropsychiatric syndromes can result from infections of the central nervous system by invading microorganisms. In addition to syphilis and influenza, infections by herpes virus, HIV, pork tapeworms, hepatitis C, Lyme disease spirochetes, group A beta-hemolytic streptococcus, and tuberculosis can present with neuropsychiatric symptomatology. Patients that have been exposed to leptospirosis have a 1.58-fold greater risk of depression than their unexposed peers [31].

Recent experiments with laboratory primates and rodents have demonstrated that a transmissible protein or prion from afflicted animals can induce brain diseases in uninfected animals [32]. By injecting "proteinaceous infectious particles" or prions, researchers were able to transmit Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and Huntington's disease to other uninfected animals.

This raises an uncomfortable question as to whether neurodegenerative disorders such as Alzheimer's disease might be infectious. The authors point out that although they have demonstrated the communicability of "pathogenic protein seeds", this does not imply that Alzheimer's disease is transmissible from person to person under ordinary circumstances [32]. The malignant proteins used in their experiments were carefully extracted from infected brain tissue and directly injected into naïve hosts.

The connection between infections and neuropsychiatric conditions is exemplified by the recent interest in obsessive-compulsive symptomology associated with streptococcal infections in children. Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) are hypothesized to result from an autoimmune reaction following an infection.

It has been observed that in a subset of children, there is a rapid onset of behavioral symptoms following an infection by group A beta-hemolytic streptococcus such as a strep throat. It appears that antigenic cross-reactivity of antibodies targeting streptococcus also attack the basal ganglia resulting in dramatic and sudden onset of behavioral tics and/or obsessive-compulsive symptoms. Additional symptoms include labile moods, anxiety, depression, irritability, and aggressiveness. These are usually abrupt in onset and not characteristic for the child. Other manifestations of PANDAS and PANS include severely restricted food intake, marked oppositional behavior, sudden regression in school performance, deterioration of handwriting, sleep disruption, and enuresis.

Latent infections with the protozoa, *Toxoplasma gondii*, have been associated with suicidal behavior, personality disorders, schizophrenia, and bipolar disorder [33]. This common parasite inhabits up to one-third of humans. It is commonly acquired from contact with the feces of pet cats or eating undercooked meat. Once inside brain tissue, *Toxoplasma gondii* can elude eradication by forming cysts or hiding in glial cells and neuronal tissue. This can lead to a chronic low-grade infection and latent activation of immunity resulting in chronic inflammation.

Recently an association was discovered between undetected *Toxoplasma gondii* infection and aggression and impulsivity [33]. Specifically a correlation between latent Toxoplasma infection and Intermittent Explosive Disorder, self-directed aggression, and suicidal behaviors were revealed.

Maternal infections during pregnancy are a well-known risk factor in offspring for the onset of schizophrenia later in life. Microorganisms such as the influenza virus, measles, rubella, polio virus, herpes simplex virus, and the toxoplasmosis protozoa infecting a pregnant woman are well-documented risk contributor for the development of schizophrenia and psychosis in progeny.

Gut microbiome: For over a century, a phenomenon of "auto-intoxication" in the human body has been associated with psychological syndromes [34]. It was believed that waste and toxins that accumulate in the intestinal tract can poison a person resulting in depression or psychosis.

In a peculiar twist, there is a resurging interest in the role of the gut in psychiatric symptomatology. The ability of the digestive tract to communicate with the brain – and the ability of the brain to communicate with the digestive tract – is known as the "gut-brain axis" [35]. This "bi-directional" communication between the gut and the brain is leading to some groundbreaking discoveries in psychiatry.

An association between the gut microbiome and first-onset of schizophrenia was recently discovered [36]. Patients experiencing their first episode of psychosis had altered intestinal bacteria composition. It appears that the gut flora changed in these patients, possibly as a result of inflammatory effects.

In addition, the administration of antipsychotic medications also affected the intestinal environment in these patients [36]. This seemed to suggest that some of the metabolic side effects of antipsychotic drugs may be due in part to the medication's impact on the gut microbiome. It also raises an interesting strategy for addressing metabolic problems of antipsychotic medications by correcting intestinal microbiota composition with probiotics or fecal transplants.

The human intestine is inhabited by over one quadrillion viruses and over 100,000,000,000,000 bacteria. The human body contains ten times more bacterial cells than human cells. There are 150 times more bacterial DNA in our bodies than human DNA. It is hard to refute the crucial role that this biomass exerts on our physiology and our psychology. We are vastly outnumbered.

The human body coevolved with microorganisms. Because of our longstanding symbiotic and reciprocal relationship to these microbes, they are often referred to as "old friends" [37]. They have been a part of us for as long as we've been a multicellular organism. We are the host and they are our welcome guests.

There are over 1,000 different species of bacteria, viruses, protozoa, and fungi in our gut. The human body is covered in microbes. Every surface of our body – skin, eyes, ears, nose, mouth, sinuses, lungs, bladder, vagina, etc. – has a native microfauna population.

Even the human brain, once thought to be sterile, may have its own normal flora. Recently bacterial RNA has been discovered in autopsied brains [38]. RNA sequences from a common soil bacterium, α-proteobacteria, have been isolated from white matter tissue suggesting a distinct microbiome of the brain. It has long been known that viruses can inhabit brain tissue. Viruses such as herpes, cytomegalovirus, and HIV are routinely found in the brains of infected persons as has the protozoa *Toxoplasma gondii*.

The intestines have the densest concentration of microorganisms in the body. There is as much as six pounds of bacteria in our intestine and colon. Over 70 percent of the human immune system is also located in the walls of our intestines. The substantial colony of organisms inhabiting our bodies is referred to as the microbiome. It is suggested that the microbiome is itself an organ of the body due to its indispensable role in human physiology.

Traditionally microbes were considered invaders rather than normal flora. Microorganisms were seen as pathogens that needed to be eliminated. It is

now becoming clear that there is a symbiotic relationship between microorganisms and their host. It is a mutually beneficial relationship.

Hygiene hypothesis: The Hygiene Hypothesis proposes that modern man's preoccupation with eliminating exposure to microorganisms has led to the development of countless autoimmune disorders, unchecked inflammatory conditions, and lethal allergies. This hypothesis was developed following observations that improved sanitation and personal hygiene in childhood resulted in increased allergies and autoimmune disorders in adulthood [39].

It is now thought that childhood exposure to microbes can "train" our immune system. Our bodies need to be taught what is foreign and what is indigenous. The immune system must be primed through a process of repeated exposure to microbes in order to distinguish between host and intruder.

The relevance of microbial exposure in children led to an interesting observational study conducted in Sweden. Researchers compared the prevalence of allergies in children who ate off of plates that were cleaned in a dishwashing machine versus hand-washed dishes. The contact with microorganisms in the less sanitized hand-washed dishes, cups, and utensils conferred some protection against the development of allergies and autoimmune disorders compared to machine washed dishware [40].

The authors also observed that if children ate foods that were fermented or foods that were obtained directly from farms, the risk of allergies was further decreased. The effect of this microbial contact with fermented foods and farm-direct foods even demonstrated a dose-response correlation [40].

In an even more recent study, a hypothesis was tested that suggests microbial exposure from thumb-sucking or nail-biting might provide some protection against autoimmune disorders later in life. The researchers found that children who sucked their thumbs or bit their nails had a lower risk of developing asthma, hay fever, and atopic sensitization in adulthood than their same age cohorts [41].

Within the first few minutes of life, a baby is exposed to microorganisms. This encounter establishes their microbiome. While in the womb, a developing fetus is in a sterile environment. Upon birth, the newborn is immediately inoculated with microbes from the mother's vagina.

When a child is born by C-section, it is under a sterile procedure. The baby is not exposed to the indigenous microbes of the birth canal. They do not get to develop a normal human microbiome but rather are exposed to non-commensal bacteria from the surrounding environment. Babies that were born by C-section suffer disproportionally from allergies, asthma, diabetes, celiac disease, eczema, and other autoimmune disorders [42].

Since the rate of Cesarean deliveries has increased by over fifty percent in recent years, research into the long-term consequences are being investigated. In particular, the psychiatric sequelae for individuals who were born in a sterile environment are in forefront of this research.

In addition to C-sections, babies that are bottle fed rather than breast fed are also not benefiting from the normal exposure and inoculation of indigenous organisms from the mother. Babies that do not have this early contact with symbiotic bacteria tend to have lower counts of normal organisms such as Bacteroides and higher colonization with pathogenic organisms such as *Clostridium difficile* [43].

The importance of early exposure to normal microbes has led to some innovative research where swabs of a mother's vagina are used to inoculate a baby's mouth, eyes, and skin immediately following a sterile birth [43]. This vaginal microbial transfer, or "vaginal seeding", is meant to stimulate the normal development of a microbiome in the newborn following a C-section.

Pacifier cleaning practices have also been shown to deter the development of allergies. Babies whose mothers "cleaned" their pacifiers by sucking on them demonstrated lower rates of asthma, eczema, and other sensitivities [40]. It appears that a parent's oral microbiota is transferred by saliva to the baby when they suck on the pacifier to clean it. This transfer of salivary microorganisms seems to prime the immune system which in turn reduces the risk of developing subsequent allergies.

The importance of early exposure to microorganisms in regulating the immune system has been demonstrated with children who live with dogs. Children raised in households with dogs have a distinct microbiome composition. Since dogs have diversified contact with soil and other natural environmental fomites, they can inoculate family members to naturally occurring commensal bacteria.

It appears that physical interaction with dogs has an impact on the host-immune response. In addition to an enriched gut microbiome, exposure to dogs in early infancy has been demonstrated to reduce the risk of developing allergies [44]. In particular, dog contact has been proven to protect against airway allergen sensitivity and asthma. One bacteria species that seems to be critically important in mediating this immune function is *Lactobacillus johnsonii*.

Psychobiotics: Disrupted microbiomes have been identified in patients suffering from autism and depression [35]. Patients with autistic spectrum disorders are well known for having gastrointestinal disorders. In particular, an abundance of Clostridia species are often isolated from the intestines of patients with autistic spectrum disorder.

In an effort to improve the symptoms of autism, a group of researchers are investigating the feasibility of altering and restoring the microbiome of the gut [45]. Several interventions are being considered, including fecal transplants, to recolonize the intestine and restore a healthy gut flora.

By exposing laboratory mice that had autistic traits to probiotic bacteria, their behavior was improved. Hsiao et al [46] gave an oral inoculation of the commensal bacteria, *Bacteroides fragilis*, to the autistic mice. Improvements in stereotypic actions, anxiety behaviors, communication deficiencies, and sensorimotor problems were observed following the restoration of the microbiome by exposure to this bacterium.

In another experiment, exposing mice to the common intestinal bacteria, *Lactobacillus rhamnosus*, reduced their anxiety behaviors and improved their depression-like actions [47]. The researchers found that consistent exposure to *Lactobacillus rhamnosus* resulted in positive changes in GABA receptor stimulation and GABA metabolism in the prefrontal cortex, hippocampus, and amygdala.

Exposure to a probiotic containing *Lactobacillus rhamnosus* GG strain was also found to attenuate obsessive-compulsive behaviors in mice [48]. Since microorganisms and their metabolites can affect satiety signals and eating behavior, it is not surprising that fecal transplants from obese mice induced hyperphagic behavior and obesity in previously germ free mice. Microbiota transplantation from lean individuals is being explored as a possible treatment for obesity in medically uncompromised patients.

An experimental comparison of a probiotic versus an antidepressant was trialed in an innovative study [49]. In most measures of stress-related behaviors, inoculation with the bacteria, *Bifidobacterium longum*, surpassed the effects of escitalopram (Lexapro) in reducing anxiety and depression.

The positive effects of normalizing the microbiome and the potential of probiotics and fecal transplants in treating mental illness are leading to some unconventional discoveries and novel approaches for therapy. It has been found that probiotic bacteria can produce monoamines and neurotransmitters such as GABA and serotonin. In addition, these bacteria can exert anti-inflammatory effects on the immune system. These microbes can also diminish activation of the hypothalamic-pituitary-adrenal axis.

A new field is emerging called psychobiotics [42]. Psychobiotics are live microorganisms that are administered to increase the wellbeing of an individual that is suffering from psychiatric symptoms. These symbiotic microorganisms have been demonstrated to relieve depression, anxiety states, and chronic fatigue symptoms. They seem to function by communicating with the brain through the vagus nerve, spinal cord, and the endocrine system [42].

An even more radical intervention involves the deliberate infestation of a person with intestinal worms. The immune system of mammals evolved over thousands of years while they were simultaneously infected with parasitic worms. In order for these worms to survive rejection by their mammal hosts, they had to evolve an ability to suppress immune attacks.

Human helminth therapy exploits the fact that these worms secrete potent immune modulators. These parasites seem to control excessive inflammation and decrease autoimmunity and antigen reactivity. Researchers at Duke University are planning a clinical trial to see if infestation with these worms can be used to treat depression [50].

Two species of helminths are currently being used to colonize the intestine, *Trichuris suis* (pig whipworm) and *Necator americanus* (human hookworm). Hookworm larvae are even available commercially and can be purchased on the internet for people seeking unconventional immunosuppression.

MECHANISMS OF ACTION

Blood-brain barrier

The regions of the brain that are particularly susceptible to inflammation are also involved in arousal and alarm. Subcortical areas like the basal ganglia and cortical circuits such as the amygdala, anterior cingulate cortex, and anterior insula can be affected by neuroinflammation.

Activation of the immune system and inflammation in response to stressors is a crucial evolutionary adaptation. The heightened response is the body mounting an attack to invaders and pathogens. The relationship between the central nervous system and the immune system is complex. Each system influences the other. This two-way communication is referred to as "bi-directional" emphasizing the back-and-forth interaction.

At the same time, there is an iterative dynamic between inflammation and psychiatric pathology. This raises a conspicuous question as to whether inflammation causes mental illness or does mental illness cause inflammation.

Until recently, the connection between the central nervous system and the rest of the body was elusive. The brain was considered to be an isolated and protected organ. It is separated by the blood-brain barrier. The blood-brain barrier is a complicated structure comprised of specialized endothelial cells and astrocytes. This forms a tight semipermeable membrane that protects the brain from toxins, infectious agents, immune cells, and inflammatory molecules. Following injury or inflammation, the integrity of this barrier is compromised. The membrane becomes permeable to circulating antibodies, white blood cells, and immune molecules.

According to Khandaker et al. [51]: "Contrary to the traditional view that the brain is an immunologically privileged site shielded behind the blood-brain barrier, studies in the past 20 years have noted complex interactions between the immune system, systemic inflammation, and the brain, which can lead to changes in mood, cognition, and behavior."

Cytokines

The chemical messengers of inflammation are cytokines. Cytokines are protein molecules that mediate the immune response and regulate inflammation. There are numerous immune proteins in the human body but the main cytokines that interact with the central nervous system are interleukin-1, interleukin-6, tumor necrosis factor, and C-reactive protein.

During systemic inflammation, there are an excess of cytokines. These cytokines result in a group of symptoms or "sickness behaviors" which mimic depression. The symptoms include lethargy, sleep disturbances, appetite changes, amotivation, cognitive impairment, anhedonia, depressed mood, and even suicidal ideation [4].

Excess cytokines are toxic to neuronal tissue. They can produce pathological changes that affect neurotransmitter metabolism, neuroendocrine action, and synaptic plasticity [23]. Cytokines also produce oxidative damage to nervous tissue affecting their growth and survival. Oxidative stress impairs DNA replication and interferes with methylation and genetic coding. This might account for the epigenetic expression that results in the manifestation of many psychiatric disorders.

The neuronal damage is most pronounced in mood-relevant regions of the brain such as the prefrontal cortex and the amygdala [4]. Neurotrophic modulators are also impacted thereby diminishing neurogenesis and neuroplasticity. Cytokines also activate an enzyme, indoleamine 2,3-dioxygenase, which impacts tryptophan metabolism. This ultimately causes a decrease in serotonin resulting in depression. In addition to the diminished synthesis of serotonin, dopamine, and norepinephrine, inflammation also results in disruptions of monoamine reuptake transporters further impairing neurotransmission.

Microglia

Within the central nervous system, the functions of macrophages are carried out by specialized cells called microglia. Microglia cells provide the immune defense of the brain. Microglia can inactivate infectious agents, scavenge damaged tissue, disable toxins, and remove plaque. These microglia cells comprise as much as 15% of human brain tissue. When injury or invasion is detected, microglia cells will transform and proliferate and go on the attack. Together with the release of cytokines, the activation of microglia cells can degrade the tissue comprising the blood-brain barrier leading to increased permeability further exposing the brain to inflammatory molecules.

Elevated microglial activity has been observed in the prodromal phase of schizophrenia [52]. It might be that increased activation of microglia cells portends the onset of schizophrenia. The immune abnormalities discovered in patients suffering from schizophrenia present a promising opportunity to trial immunosuppressive agents. It has even been suggested that administering monoclonal antibodies that target cytokines and cytokine receptor sites could help neutralize an over activated immune response and result in significant improvements in cognitive functions [52].

There are many external causes of inflammation. The most common is an infection. After all inflammation is the reaction of the immune system as it mounts a response to an invader. In addition, toxins, noxious dietary substances, pollution, and physical trauma can also set off an exaggerated inflammatory reaction.

Adverse childhood experiences and psychosocial stressors are also well known catalysts for prolonged inflammation. The immune system can sometimes overreact to psychological stressors producing a disproportionate response. This has led some researchers to view the body's response as an "allergy to stress" [30].

Obesity can also be a cause of prolonged inflammation. Adipose tissue produces and secrets cytokines and immune molecules which potentiate chronic inflammation [4].

Enteric nervous system

The relationship between the human gut and the central nervous system goes back to the early development of the fetus. During the formation of the embryo, nerve cells and intestinal cells begin as the very same mass of tissue. It is only in later developmental stages of the embryo that these cell lines begin to differentiate.

Many nerve cells remain embedded in the intestinal tract of the fetus. This becomes the Enteric Nervous System. Sometimes referred to as the "second brain", the Enteric Nervous System contains over 100 million neurons – as many neurons as in the peripheral nervous system.

There are several neurotransmitters produced in the gut. Over 90% of serotonin in the human body is produced in the intestinal tract. There are numerous types of serotonin receptors in the gut alone and they appear to play a critical role in digestion.

The brain is directly connected to the gut by the vagus nerve – cranial nerve X. The vagus nerve is the longest cranial nerve in the human body. This nerve is bidirectional in that it conveys visceral information to the brain and information from the brain to the gut becoming the gut-brain axis.

The psychoactive effects of the gut microbiome are communicated to the brain via the vagus nerve. When the vagus nerve is experimentally amputated in mice, the neurochemical and behavioral influences of the microbiome abruptly discontinue [47].

Microorganisms in the intestines produce biologically active neurochemicals. GABA, serotonin, acetylcholine, and catecholamines have

all been isolated from bacteria inhabiting the human intestine [53]. Other microbial metabolites such as tryptophan derivatives and short-chain fatty acids can cross the intestinal barrier, enter the bloodstream, and penetrate the blood-brain barrier and act as neuroactive mediators. This is one of several mechanisms which might account for the effects of psychobiotics.

There may also be lateral gene transfer where genetic material of bacteria can be transferred or transmitted to human cells. This can result in remodeling of genetic coding, transcription and translation errors, insertional mutations, and ultimately altered expression of genes in the human host. This is not unlike the lateral gene transfers between viruses such as human papillomavirus, Epstein-Barr, and hepatitis B which infect and alter the human chromosome.

Intestinal worms secrete a variety of molecules and proteins. These chemicals have immunomodulatory and anti-inflammatory effects [39]. In order for helminths to survive inside mammals, they had to evolve in such a way that they can evade detection by the host's immune system. It has been suggested that helminths adapted by producing potent anti-inflammatory compounds.

The symbiotic relationship between humans and microorganisms is crucial for the development of the immune system. Epidemiological comparisons of the rates of autoimmune disorders in poor countries versus industrialized countries led to the development of the "Hygiene Hypothesis".

It appears that routine exposure to microbes as a child in countries with less developed sanitation systems trains the immune system. The "Hygiene Hypothesis", also known as the "biome depletion theory", suggests that immunity is primed by exposure to a diverse microflora.

In countries with improved sanitation, increased use of antiseptic cleaners, and frequent use of antibiotics, an "immune tolerance" does not develop. This leads to an overactive immune system resulting in increased allergies, autoimmune diseases, and inflammatory conditions.

Increased permeability of the intestine is often observed in patients who are depressed [4]. This exposes the general circulation to the contents of the bowel. Inflammatory molecules can affect the integrity of the intestinal wall causing a "leaky gut". These patients often have an increased antibody response directed at commensal gut bacteria.

A leaky gut and neuroinflammation have been implicated in the onset of Parkinson's disease. Inflammation attacks dopamine producing cells in the brain causing motor deficits. It has been observed that many patients diagnosed with Parkinson's disease first present with constipation and gastrointestinal problems.

TREATMENT IMPLICATIONS

Nonsteroidal anti-inflammatory drugs (NSAIDs)

The relationship between psychiatric disorders and inflammation seems to suggest an unconventional alternative for treating mental illness. It appears that the immune system could be tamed or moderated. In addition to conventional therapeutics for treating psychiatric symptomatology, should treatment strategies include augmentation with an anti-inflammatory agent? While factions in the research community debate and speculate, clinicians await guidance on whether to use immunotherapy in addition to, or rather than, psychotropic medications [29]. Anti-inflammatory medications – either as monotherapy or as adjuncts – have demonstrated a modest effect in mitigating psychiatric symptoms [54]. The use of NSAIDS as an adjunct to antidepressant medication has demonstrated improved responses without significantly increased adverse effects.

When antidepressants fail to induce remission, it might be that the premise of neurotransmitter depletion is incomplete. By only targeting serotonin and dopamine, the effects of inflammatory cytokines causing neurochemical imbalance is left unaddressed [30].

It has been shown that antidepressant medications, particularly SSRIs, as well as some antipsychotic drugs and mood stabilizers, have intrinsic anti-inflammatory properties. The immune suppressing actions of these drugs might even explain some of their therapeutic action [2]. Fluoxetine and trazodone appear to protect neurons from cytotoxic effects by decreasing inflammatory mediators and regulating neurotrophic growth factors [55].

In a double-blind, randomized, placebo controlled study, adjunctive use of the NSAID, celecoxib 400 mg/day, produced a rapid onset antidepressant effect in bipolar disorder patients having depressive or mixed episodes [56]. Improvements were seen in the very first week of treatment. Celecoxib was well tolerated in this study.

The tetracycline antibiotic, minocycline, has been shown to exert anti-inflammatory properties. In addition, minocycline can cross the blood-brain barrier. In a double-blind, randomized, placebo-controlled study with patients suffering from schizophrenia, minocycline 200 mg/day demonstrated improvements on general outcomes, negative symptoms, and cognitive functioning. Minocycline was well tolerated [57]. The researchers concluded that minocycline was a beneficial add-on treatment in schizophrenia.

Low dose aspirin (81 mg/day) has also demonstrated reliable results as an adjunctive treatment in depression [25]. Ibuprofen also reduced the chances of seeking psychiatric care in this study. The sample size for this study was a quarter of the population of Denmark (5.5 million people). Low dose acetylsalicylic acid, acetaminophen, and ibuprofen were assessed as adjuncts to SSRI medication. The researchers concluded: "Especially low-dose acetylsalicylic acid may represent an adjunctive antidepressant treatment option" [25].

Low dose aspirin also shortened the onset of action for SSRI antidepressants. In the treatment of depression, the combination of low dose aspirin (160 mg/day) along with an SSRI accelerated the onset of the antidepressant effect, increased the rate of remission, and improved the response rate [58]. A significant improvement was observed within the first week of augmentation.

It is interesting to note that the sample population for this study included patients that were non-responders to SSRI medication and had been on an adequate trial of the antidepressant for 4 weeks prior to receiving aspirin. In conclusion, the researchers were in favor of using aspirin for its accelerating effect in combination with SSRIs for the treatment of major depression [58].

In another study, the use of aspirin was shown to decrease the risk of depression in older men [59]. The antidepressant effect was particularly notable in men with an increased inflammatory marker, homocysteine. In this investigation, aspirin was used as a standalone treatment. It was a monotherapy and not used in combination with any antidepressant medication.

In a double-blind, placebo-controlled investigation with 70 patients diagnosed with schizophrenic and receiving antipsychotic medication, individuals that were randomized to supplemental aspirin (1,000 mg/day) demonstrated an improvement in psychopathology [26]. The authors concluded: "Aspirin given as an adjuvant therapy to regular antipsychotic treatment reduces the symptoms of schizophrenia. The reduction is more pronounced in those with the more altered immune function."

In Alzheimer's disease and mild cognitive impairment, long-term use of NSAIDs has been shown to protect patients from developing further neurodegeneration later in life [27]. The anti-inflammatory action of NSAIDs seems to prevent the buildup of β-amyloid plaque in brain tissue if used in the very early stages of Alzheimer's disease and mild cognitive impairment.

Immunotherapy

Since PTSD is associated with measurably increased inflammation, could this present a revolutionary approach to treatment? It has been suggested that the chronic low-grade inflammation seen in PTSD could provide a promising target for medication management [11].

In addition, the elevated levels of inflammatory markers found in the brains of victims of suicide are a provocative finding [12]. In addition to predicting suicide by testing for elevated markers, treating inflammation

could represent a new frontier in medical therapeutics for self-destructive behavior [60].

Anti-inflammatory agents used to treat allergies have had the unintended effect of reducing the risk of suicide. Intranasal corticosteroids prescribed to treat allergic rhinitis have resulted in a reduction of the suicide rate among its users [61].

Over activation of the immune system as evidenced by elevated C-reactive protein is a potential target to reduce psychiatric symptomatology. Statin medications have long been used to reduce this biomarker. Vitamin C can also be used. In one study, 1,000 mg per day of vitamin C reduced C-reactive protein by over 25 percent. Vitamin C is as effective as statins to reduce C-reactive peptides [62].

Omega-3 fatty acids

There are also non-pharmacologic measures that can help reduce the immune system's activation of C-reactive protein such as increased intake of low glycemic food, increased physical activity, improved dental hygiene, enhanced sleep, and supplemental Omega-3 Essential Fatty Acids [63].

Omega-3 Fatty Acids are well known for their reliable anti-inflammatory properties and suppression of cytokines. Like many common anti-inflammatory drugs, Omega-3 Fatty Acids interact with the enzyme cyclooxygenase-2 (COX-2) and thereby have an effect on prostaglandin. Omega-3 Fatty Acids also exert their immune modulating effects through the expression of inflammatory genes and the activation of transcription factors and other inflammatory mediators.

A lengthy meta-analysis was undertaken by the American Psychiatric Association's Committee on Research on Psychiatric Treatments in 2006 [64]. The researchers reviewed numerous controlled studies that explored the role of Omega-3 Fatty Acids in various psychiatric disorders. The authors noted: "The evidence in favor of omega-3 EFA as a putative psychotropic is preliminary but encouraging, and the possible wide range of indications for omega-3 EFA is especially exciting, particularly in view of the high tolerability and apparent safety."

Under the Conclusions section of the Omega-3 Fatty Acids: Evidence Basis for Treatment and Future Research in Psychiatry study, the authors state: "The preponderance of epidemiologic and tissue compositional studies support the protective effect of omega-3 EFA intake, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in mood disorders. Meta-analyses of randomized controlled trials demonstrate a statistically significant benefit in unipolar and bipolar depression."

Regarding schizophrenia, Freeman et al. [64] observed that patients who were prescribed Omega-3 Fatty Acids exhibited significantly lower scores on the Positive and Negative Syndrome Scale by the end of the study regardless of variations in antipsychotic medications.

In the section on ADHD and Learning Disabilities, these authors noted that Omega-3 supplementation for just four months demonstrated improvements in teacher-rated attention and parent-rated conduct. There was also an improvement in behavior of children whose behavior met the clinical criteria for oppositional defiant disorder.

Freeman et al. [64] further state: "Considering the risks of comorbid obesity and cardiovascular disease and the risk profiles of some psychotropic agents, omega-3 EFA may play an important role in our patients' health. Omega-3 EFA may reduce the risks of diabetes mellitus and hypertriglyceridemia associated with some atypical antipsychotic treatment, as well as the obesity that is often comorbid with psychiatric disorders."

Supplementation with Omega-3 Fatty Acids appeared to have negligible risks [64]. Adverse events were infrequent and minor in the studies investigated above. In general, supplementation was well tolerated in almost all of the research that was analyzed.

In a study conducted in 2007 which examined the management of self-harming behaviors and major depressive disorder, the researchers found robust evidence for supplementation noting that the effects of these fatty acids were at least as great, if not greater than, antidepressant medications [65].

In the analysis of Borderline Personality and Impulsivity, Freeman et al. state [64]: "In a placebo-controlled trial of 30 patients with borderline personality disorder, significant decreases in aggression and hostility measures were reported for monotherapy treatment with 1 g/day of [omega-3] EPA."

This conclusion referenced an eight-week double-blind study published in the American Journal of Psychiatry of Omega-3 Fatty Acid supplementation with women diagnosed with Borderline Personality Disorder [66]. The researchers of this investigation concluded that Omega-3 Fatty Acids were superior to placebo in diminishing aggression as well as depressive symptoms and may be a safe and effective form of monotherapy for women with borderline personality disorder.

Anti-Inflammatory lifestyle

Another natural remedy that has demonstrated potential as a safe and effective anti-inflammatory agent is curcumin. Curcumin is the bioactive phenol found in the spice turmeric (*Curcuma longa*), a member of the ginger family. As an antidepressant, curcumin exerts its effect through several mechanisms. In addition to its anti-inflammatory action and inhibition of cytokines, curcumin is a potent antioxidant. It also increases neurogenesis, increases brain-derived neurotrophic factor, and affects serotonin and dopamine transmission [67]. Curcumin also has a moderating effect on the hypothalamic-pituitary-adrenal axis.

With increasing interest in natural treatments for depression, and efforts to enhance current treatment outcomes, curcumin is presented as a promising novel, adjunctive or stand-alone natural antidepressant [67]. As a result of the popularity of curcumin, many formulations are now available as a nutritional supplement. Because curcumin is not easily absorbed from food, special over-the-counter herbal formulas have been prepared that are more bioavailable and better absorbed. Even in high doses, this phenol has very few side effects.

Among the lifestyle interventions known to affect inflammation, it is well known that the human diet exerts considerable effect. A diet that is high in sugar, refined grain, processed meat, and trans-fatty acids is pro-inflammatory while a diet that is high in whole vegetables, unprocessed fruit, and whole grains can reduce inflammation.

The positive effects of exercise on depression are also well known. It now appears that part of exercise's mood boosting actions are a result of reducing inflammatory cytokines. Physical exercise also decreases proliferation of microglia in the brain and modulates the activation of microglia cells [68]. Physically active people consistently demonstrate reduced levels of inflammatory biomarkers compared to their sedentary peers and this likely accounts for the reliable antidepressant effects of exercise [4].

Another way to tame the immune system is through therapeutic human interaction. Psychotherapy itself can exert anti-inflammatory effects. In an innovative pilot study of women experiencing depression, cognitive behavioral therapy was able to reduce inflammatory biomarkers. After the seventh session of cognitive behavioral therapy, measurable decreases from prior baseline levels of interleukin-6 were detected in the study participants [69]. These subjects did not receive any other medications to account for the immune modulating effects of the therapy.

Probiotics

The emerging field of psychobiotics – ingesting live microorganisms – that provides benefits to individuals suffering from psychiatric illness attributes its effects to the mediation of inflammation [42]. In addition to the neuroactive compounds secreted by these microbes, such as GABA, serotonin, acetylcholine, and catecholamine, psychobiotics also reduce neuroendocrine activity in the hypothalamic-pituitary-adrenal axis.

Inoculation with selected probiotic strains has demonstrated both antidepressant and anxiolytic effects in subjects. These effects are due to the microbes' ability to modulate an over-active inflammatory response in individuals. Correcting or enhancing a person's microbiome can be accomplished by eating fermented foods, ingesting live probiotics,

consuming pre-biotics (plant fibers that nourish commensal microbes), taking antibiotics (to kill pathogenic bacteria), or receiving fecal transplants from healthy donors [70].

Microbial diversity should be the goal in microbiome enrichment. A well-populated gut is a healthy gut. Although numerous strains of intestinal bacteria can modulate inflammation, a couple of strains have been studied more extensively. Augmentation with *Lactobacillus rhamnosus* has been shown to be an effective adjunct to antidepressant medications [47]. Exposure to *Lactobacillus rhamnosus* produced positive changes in GABA metabolism and GABA receptor stimulation in the prefrontal cortex, hippocampus, and amygdala.

Another bacteria species, *Bifidobacterium longum*, demonstrated positive impact on cognition [71]. This same strain, *Bifidobacterium longum*, was used in an experiment on anxiety comparing this probiotic against a conventional antidepressant. In some metrics of stress-related behaviors, exposure to *Bifidobacterium longum* outperformed escitalopram [48].

In a randomized placebo controlled trial of probiotic supplementation, exposure to *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* probiotics was associated with lower rates of re-hospitalization as well as shorter inpatient admissions [72].

Proper exposure to commensal microorganisms at birth is critically important to developing a healthy microbiome. In a sterile birth procedure such as a C-section, the baby is not exposed to the indigenous microbes of the birth canal. The baby will not be colonized with a normal microbial fauna. Instead the newborn will be exposed to non-commensal bacteria from the environment. Newborns that were born by C-section are disproportionally affected by allergies, asthma, diabetes, celiac disease, eczema, and other autoimmune disorders [42].

An innovation to initiate normal colonization with healthy bacteria in babies born by C-section uses swabs of a mother's vagina to inoculate a baby's mouth, eyes, and skin immediately following a sterile birth [73]. This practice, referred to as "vaginal seeding" or vaginal microbial transfer, can initiate the development of a healthy microbiome in the newborn and hopefully prevent the onset of autoimmune disorders later in life.

Physical contact with dogs in early childhood has been shown to cultivate a competent host-immune response, enhance the gut microbiome, and reduce the risk of developing allergies [74]. Since dogs have uninhibited contact with soil and the natural environment, they are an important fomite for enhancing the microbiome of family members with naturally occurring commensal bacteria.

One bacteria species in particular that dogs can expose its handlers to is *Lactobacillus johnsonii*. This microorganism seems to play a critical role in mediating this immune function and protecting against allergies and allergen sensitivities. There are commercially available probiotics of this bacterial strain available for this purpose.

Finally, it is important to caution that not all individuals who have excessive inflammation will suffer from mental illness. At the same time, not all individuals with psychiatric symptoms will have elevated inflammatory biomarkers. Therefore not all individuals with mental illness will demonstrate improvements with anti-inflammatory therapy. It has been found that psychiatric patients with measurably elevated immune markers are the most responsive to anti-inflammatory agents as adjunctive therapy [9].

This suggests that a diagnostic blood test for inflammatory biomarkers could predict response and inform therapeutic decision making. By testing for inflammation, a subgroup of responders can be identified [75]. Research seems to indicate that there is a subset of patients with whom anti-inflammatory augmentation will most benefit.

It appears that some patients that are treatment resistant to conventional medication regimens can benefit from augmentation with an anti-inflammatory agent. Kiecolt and Derry [4] noted that for patients with major depression who had elevated inflammatory markers, responsiveness to conventional antidepressant medications may be poorer.

CONCLUSION

The study of the human brain is still a relatively new science and recent research and radical discoveries are challenging established theories. The brain is the most elusive organ in the human body. The current state of neuroscience involves a great deal of speculation and conflicting theories. Many current interventions in psychiatry were serendipitous and accidental discoveries. They did not arise out of rational investigations based on cogent theories.

A convergence of several ground-breaking discoveries are trending toward a watershed moment in psychiatry. A reconceptualization of the disease model for mental illness may replace the monoamine paradigm and the outdated theories of neurochemical depletion. A revolution in neuroscience is emerging – an intersection between immunology and neuropsychiatry. The mechanism for the mind-body synergy is beginning to be elucidated.

The scientific momentum gathering around the inflammation hypothesis in psychobiology signals an exciting approach for understanding the pathogenesis of mental illness. The presence of chronic inflammation and its unchecked biochemical cascade in many disease states – not just mental illness – contribute to the deterioration and exacerbation of symptomatology. Inflammatory biomarkers present a revolutionary target and a promising role for anti-inflammation strategies as part of developing a treatment regimen.

The specific underlying mechanisms between inflammation and mental illness are yet to be fully described and many of the observations thus far should not be taken as proof of cause-and-effect. There are many unidentified downstream effects and confounding correlations. However the therapeutic implications for addressing inflammation are exciting. Now that a proof-of-concept has been established for the role of controlling inflammation, a testable hypothesis is available for further exploration. Moderating an over-active inflammatory response will be the new frontier for pioneers in psychiatry. Taming the immune system will offer promising innovations and holds the potential to transform the science.

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