Acupuncture for the Treatment of Autoimmunity: Mechanisms and Perspectives

MS-PREP Capstone Project
Spring 2017
Meghan Meade, L.Ac., MAOM.
Amy Jo Accardi, L.Ac., MSAOM.
Libby Bradshaw, D.O., MS.

ABSTRACT

Autoimmune disease represents a growing collection of complex, multi-etiological disorders for which there is no known cure. Despite being the subject of ongoing research continually yielding new insights into autoimmune pathology and treatment, the impact of autoimmune disease is significant, and many patients' needs are left unmet. Autoimmune disease patients may experience vague, relapsing-remitting symptoms, often contributing not only to difficultly in obtaining a diagnosis but also to disjointed care, as their varied clinical presentations may lead them to seek care from multiple specialists. These factors, coupled with the significant side effect profiles of current standard of care regiments, reflect a deficiency in patient care that could be remedied through complementary, patient-centric healing modalities. To that end, this paper investigates the role of acupuncture, an ancient mind-body therapy, as a potential vehicle for relief of four common features of autoimmunity: inflammation, stress, gut dysbiosis/intestinal permeability, and pain.

INTRODUCTION

Having reached 5% worldwide[1] prevalence, autoimmune disease represents a growing challenge to the medical community and general population. More than 100 autoimmune diseases have been identified[2], and many have experienced rapid growth in recent decades.[3] The risk of developing an autoimmune disease in the United States has surpassed that of both cardiovascular disease and cancer[1], and its economic burden has nearly doubled that of cancer,[4] underscoring the need for deeper understanding of the mechanisms by which the body

misrecognizes and attacks its own tissues. Typically chronic and requiring lifelong treatment,[5] autoimmune diseases can affect every organ system in the body, and their physical, functional, social, mental and emotional influences on both patients and their families are unduly devastating.

The rise in autoimmunity has paralleled the shift towards Westernization in recent years; while industrialized nations have benefitted from improved socioeconomic status, enhanced sanitation and hygiene standards, technological advances, and a decreased infectious disease burden, they have also suffered unanticipated negative consequences in the form of heightened psychosocial stress owing to a collective cultural emphasis on economic productivity, adoption of a highly processed, sugar and fat-laden diet, decreased physical activity, and increased exposure to chemical pollutants, xenobiotics, and other toxicants.[3,5,6,7,8] Taken together, these factors stress the body in ways to which it is not evolutionarily accustomed; whereas the collective focus on productivity and economic gain creates undue psychological stress, poor diet and inadequate exercise lead to obesity and altered gut microbial profiles, predisposing towards autoimmunity;[5] furthermore, improved sanitation has yielded an unintended effect of allowing the immune system to shift focus towards endogenous constituents, leading to the hallmark of autoimmunity: immune misrecognition of self-proteins as 'foreign' via loss of self tolerance.[5,7] Moreover, new insights about the inflammatory and immunostimulatory effects of pollutants, xenobiotics, overmedication, and toxicants and their involvement in autoimmune pathogenesis are continually being uncovered. These insights, coupled with the observation that the rise in autoimmunity in westernized nations has been unparalleled by any appreciable genetic shifts

further supports the role of environmental factors over genetic factors as causative agents in the development of autoimmunity.[3,5]

Autoimmune diseases are notoriously difficult to diagnose and treat, owing to often vague and relapsing-remitting clinical presentations that may mimic numerous other conditions, and to the fact that the symptomatology of any given autoimmune disease may span multiple clinical specialties, placing these conditions - and the patients who suffer from them - at odds with the highly segmented and specialty-driven western biomedical paradigm in which they're treated. Furthermore, the inherently stressful nature of autoimmune conditions increases susceptibility to co-morbid stress and mood disorders such as anxiety and depression, calling to attention the need for comprehensive care that addresses not only the physiological but also the psychoemotional aspects of chronic illness. Compounding these challenges are the current biomedical treatments which, despite some efficacy in certain instances, carry heavy side effects and broadly suppress the immune system, rendering patients vulnerable to infection.[9]

Though an understanding of autoimmune pathogenesis and by extension, optimal treatment, is still in its nascent stage, care for autoimmune disease patients need not suffer. Treatment that includes therapeutic complementary modalities that address the common features of autoimmunity - inflammation, stress, gut dysbiosis, and intestinal permeability, and pain - while minimizing side effects should be prioritized so as to best meet the needs of the autoimmune disease patient. To that end, the ancient Chinese healing practice of acupuncture, which uses the insertion of fine needles into designated acupuncture points on the body to evoke a balancing and restorative response, will be examined as a complementary treatment avenue for autoimmune disease patients. Poorly understand by the research and medical communities, this

paper will shed light on the mechanisms by which acupuncture exerts its anti-inflammatory, anti-stress, and analgesic effects, and disseminate the ways in which acupuncture may yield physical, as well as psychological and emotional, benefits for the autoimmune disease population.

METHODS

An extensive literature review utilizing the online databases PubMed, ScienceDirect, Web Of Science, and Google Scholar was performed. An initial exploration of the research literature pertaining to autoimmune epidemiology and autoimmune pathogenesis revealed four major common threads that comprised the basis of the background section on autoimmunity: inflammation, HPA axis dysregulation, gut dysbiosis/intestinal permeability, and pain. A second exploration of the research focused on acupuncture physiology as it pertains to general mechanisms as well as in relation autoimmune disease, the immune system, and the above-mentioned common threads of autoimmunity. Search terms utilized for both autoimmunity and acupuncture research are attached separately. In light of the paucity of research on acupuncture within the context of autoimmunity, articles not explicitly related to autoimmunity but bearing relevance to the topic were included, namely studies focused on immune system function, chronic pain conditions, psychiatric mood disorders, stress, allergic diseases, and other non autoimmune chronic illnesses. Articles were reviewed for relevance, clinical applicability, language, and date. Given that both autoimmunity and acupuncture represent continually-evolving fields of study, preference was given to publications written in the past 5 years, with 2002 (15 years) serving as the cutoff date for inclusion. Other exclusionary criteria included non english language, publications for which only the abstract was available, case series, and case reports. Preference was given to human and animal studies over in vitro studies; as it relates to

study design, the following study designs were prioritized in descending order: meta-analyses, systematic reviews, randomized controlled trials, review articles and textbook chapters, and observational studies, both prospective and retrospective. Each article was read once for general thematic takeaways, a second time for greater depth of detail, and then summarized in a document designated for notes. Notes documents were organized according to background (autoimmunity) or results (acupuncture) status, and further subdivided according to theme: inflammation, HPA axis dysregulation, gut dysbiosis/intestinal permeability, and pain, for a total of eight primary reference documents. Additional reference documents included material on research methods and autoimmune epidemiology. These documents formed the basis of the six educational modules that constituted the capstone project, a two-pronged undertaking, the first prong assessing the landscape of autoimmune epidemiology, pathogenesis and treatment, and the second examining acupuncture mechanisms and their clinical applications in the treatment of autoimmunity.

RESULTS

Acupuncture Mechanisms of Action

Acupuncture exerts its effects through multiple mechanisms. Locally, acupuncture needling stimulates the release of vasodilatory peptides and endorphins, causing enhanced circulation and an accumulation of endorphins and their receptors, leading to peripheral opioid analgesia.[10] Acupuncture's visceral effects can be attributed to its influence on the sympathetic and parasympathetic branches of the autonomic nervous system, affecting neuronal pathways through a somatic autonomic reflex, which operates at both spinal-segmental and central levels. Spinal level effects pertain to acupuncture points needled on the trunk and occur when the

myotome or dermatome in which an acupuncture point is needled and the autonomic innervation of the target visceral organ lie within the same spinal segment. Put another way, acupuncture needling on the trunk sends an efferent signal to the spinal cord and the ensuing afferent signal travels to a visceral target within the same spinal segment as the dermatome or myotome in which the acupuncture point is located.[11] This pathway may account for, by way of example, how needling a point on the back designated for its gastrointestinal effects may achieve said effects, despite not being located near the affected visceral organs, and is responsible for autonomic effects such as regulation of heart rate, blood pressure, and gastric motility. Also at this level, acupuncture's stimulation of A-δ fibers may work to reverse long term potentiation (LTP), a characteristic of many chronic pain conditions that involves amplified pain responses, to long term depression (LTD), effectively attenuating central sensitization.[10] Central effects of acupuncture have been observed in fMRI studies that indicate acupuncture-induced activation of a number of regions in the brain, including the PAG, hypothalamus, pituitary, prefrontal cortex, insula and amygdala, among others. Acupuncture-induced sympathetic activation stimulates the descending pain modulatory system starting in the PAG, triggering the release of endorphins, serotonin, and norepinephrine.[10,12]

Variability in Response

Importantly, some of acupuncture's effects are dose and intensity-dependent, as more aggressive stimulation, typical of research acupuncture, has demonstrated a more stimulatory effect on the sympathetic nervous system, resulting in increased levels of stress hormones and activation of the descending modulatory system, whereas the milder stimulation that characterizes clinical acupuncture tends to reduce sympathetic outflow, leading to a reduction in

stress hormones and subsequent anti-stress effects.[13,10] Electroacupuncture, more commonly used in research settings than in clinical settings as a means of amplifying its effects and ensuring reliable quantification of the stimulation it delivers, also yields different results; low frequency electroacupuncture has been shown to affect activation of wider range of brain regions involved with pain, stimulating μ and δ opioid receptors to release endorphin, enkephalin and endomorphin, while high frequency electroacupuncture has been shown to stimulate kappa opioid receptors to affect dynorphin release, activating a narrower range of brain regions.[14,15]

It stands to reason that if it acupuncture effects vary according to the ways in which it is administered, physiological variance among patients may also impact results. It is generally accepted that an undefined subset of patients may be non responders to acupuncture therapy,[10] whether owing to physiological factors, belief and expectation factors, or a combination of the two. Notably, the presence of inflammation may considerably influence an individual's response to acupuncture, as a rat model of acupuncture analgesia indicated that a group of rats without inflammation included both responders and non responders to acupuncture, while inflamed rats comprising another group were all deemed responders, suggesting a potential adaptogenic effect in which the effects of acupuncture may be intensified or decelerated according to an individual's pre-existing degree of inflammation or other physiological circumstances.[13] Variations in individual response to acupuncture have also been associated with existing levels of CCK, a hormone primarily known for its gastrointestinal functions that is also implicated in neuropathic pain, as well as lymphocyte and granulocyte profiles, markers of sympathetic and parasympathetic nervous system dominance, respectively.[13,16] Lastly, the roles of expectation and belief - commonly relegated to the realm of placebo effect - may contribute to heterogeneity of

individuals' response to acupuncture. A study reported that all subjects with high expectations for benefit reported reductions in pain, though only those receiving true acupuncture demonstrated changes in the brain associated with analgesia, while those receiving sham acupuncture displayed no such shifts, suggesting that belief and expectation may confer additive benefits.[17]

Effects Relevant to Autoimmunity

The following review of acupuncture research will focus on its anti-inflammatory, anti-stress, gut microbiome-modulating, and analgesic effects so as to illustrate the multiple dimensions of its clinical utility in treating the autoimmune disease population.

Inflammation

First, as it relates to inflammation, acupuncture has been shown to modulate both the innate and adaptive branches of the immune system to regulate inflammatory responses. Acupuncture enhances activity of natural killer (NK) cells, components of the innate immune system, and upregulates mRNA expression of protein tyrosine kinase (PTK), an enzyme responsible for increasing NK activity, while downregulating mRNA expression of protein tyrosine phosphotase-1 (SHP-1), an enzyme responsible for decreasing NK activity.[18,19] Acupuncture also influences macrophages, having been shown to induce a shift from the inflammatory M1 type macrophages in inflamed muscle tissue to the anti-inflammatory M2 type, leading to reductions in inflammation and pain.[20]

With respect to the adaptive immune system, acupuncture restores balance to imbalanced helper T cell cytokine profiles, a known characteristic of autoimmune disease, having reduced the Th1 cytokines TNF-α, IL-6, and IFN-γ to restore balance in Th1 dominant conditions such as collagen-induced arthritis, a research proxy for Rheumatoid Arthritis.[18,21,22,] In a mouse model of

Experimental Autoimmune Encephalitis, a proxy for Multiple Sclerosis, acupuncture restored balance to skewed Th1/Th2 and Th17/Treg profiles, effectively reducing elevations in Th1 and Th17 cytokines IFN-γ and IL-17 and increasing Th2 cytokines IL-4 and TGF-β, as well as Tregs, relative to controls.[5] Additionally, acupuncture has been shown to be effective in suppressing IL-4, IL-10, and Nitric Oxide (NO) production in Th2 allergic conditions such as asthma and urticaria, and restoring levels of Th1 cytokines IL-1 and IFN-γ, leading to reductions in IgE antibodies and stabilizing the balance between Th2 and Th1 cytokines to ultimately reduce inflammation and disease severity.,[18,23,24] Acupuncture was also shown to regulate the balance between Th17 cytokine IL-17 and Tregs in a human model of Crohn's Disease and mouse model of asthma, ultimately attenuating inflammation by reducing IL-17 and rectifying the ratio of Th17 to Treg.[25,26] In light of the fact that the dominance of one T cell population - Th1 vs Th2, Th17 vs Treg - effectively inhibits the proliferation of the other and has been implicated in the pathogenesis of numerous diseases,[18] the demonstrated effects of acupuncture on regulating and restoring balance to skewed cytokine signatures is of significant consequence.

HPA Axis Dysregulation

Regarding the impact of acupuncture on the stress response system, acupuncture has been shown to modulate the HPA Axis to ameliorate aberrant stress hormone activity in a number of stress research models. In a chronic stress model of depression, significant reductions in ACTH and CRH levels as well as mRNA expression of CRH were observed among acupuncture-treated rats relative to stressed and untreated controls, indicating the capacity for acupuncture to blunt the stress response.[12] Notably, a series of animal studies performed by the same research team investigated the role of acupuncture administered before and after inducing chronic stress,

finding that acupuncture inhibited stress-mediated elevations in CRH, ACTH, and cortisone (the animal correlate of cortisol, referred to henceforth as CORT), and yielded long lasting relief after acupuncture treatment had ceased in the post-stress model, despite the continued application of stress.[12,27] Furthermore, acupuncture-treated rats showcased significant elevations in mRNA expression and levels of serotonin; the behavioral manifestations of acupuncture's effects on stress hormones and serotonin took the form of decreased 'depression behavior' - enhanced exploratory behavior and increased time to immobility (an indicator of despair), illustrating the potential for acupuncture to ameliorate maladaptive behavioral changes stemming from stress-mediated conditions.[12] A separate cold stress study found that acupuncture increased protein expression of the glucocorticoid receptor (GR) in the hippocampus, pituitary and hypothalamus, thereby promoting functional connectivity between GR and CORT, permitting GR's regulatory effects on the HPA axis; the acupuncture-induced GR activation resulted in decreases in CORT elevations, reduced HPA hyperexcitation, and a diminished stress response.[28] This study looked at the ACTH receptor (ACTHR) gene, variants of which are known to be associated with impaired physiological and psychological stress responses; whereas cold stress exposure increased protein expression of ACTHR in the pituitary and adrenals, acupuncture-treated rats demonstrated decreased ACTHR protein expression,[28] calling to attention a potential role for acupuncture in modulating genetic polymorphisms that confer susceptibility to ill health.

Gut Dysbiosis and Intestinal Permeability

The effects of acupuncture on gut dysbiosis and intestinal permeability, increasingly understood to be contributing factors in a number of autoimmune diseases, comprise a less-researched but growing field of interest. Acupuncture has been shown to be effective in reducing

inflammatory cytokines attributed with the development of gut barrier dysfunction and promotion of intestinal permeability, IL-6, TNF-α, and IL-12.[29,21,30,31,32] In human studies of Inflammatory Bowel Diseases (IBD) Crohn's Disease and Ulcerative Colitis, both patient populations indicated marked improvements in both inflammation and pathological tissue damage to affected areas of the intestinal tract following acupuncture treatment.[31,32] In a mouse model of endotoxemia, acupuncture reduced elevations in TNF-α and IL-8 in the intestines as well as the lungs, liver, and blood,[33] hinting at the capacity for not only local but also systemic anti-inflammatory effects. These anti-inflammatory effects are conferred by acupuncture-induced vagus nerve stimulation, which activates an cholinergic anti-inflammatory pathway to affect reductions in TNF-alpha, IL-8, and IL-6.[15,16, 60, 79, 105]

Acupuncture has demonstrated a role in modulating the tight junction proteins (TJP's) that serve the important function of regulating gut barrier permeability; acupuncture enhanced mRNA expression of TJP's zonulin (ZO-1), occludin, and claudin, preserved their structure and distribution, and attenuated their loss and redistribution owing to disease progression in human and animal models of Crohn's Disease and Ulcerative Colitis, and mouse models of hemorrhagic shock and endotoxemia (models of gut barrier dysfunction).[29,21,22,31] Worth noting is that enteric glial cells, involved with the preservation of the gut barrier, showed significant activation in response to acupuncture relative to sham and untreated controls,[29] indicating that acupuncture's impact on gut barrier integrity operates through multiple mechanisms. Concerning the intestinal flora, pathological aberrations of which have been linked to numerous autoimmune diseases, acupuncture increased levels of beneficial bifidobacteria and lactobacillus, and decreased levels of pathogenic B. fragilis and E. coli among rats with Ulcerative Colitis, effectively modulating

gut flora in such a way that restored balance to previously dysbiotic gut profiles, and attenuating the progression of pathology in the gut.[34] Additionally, acupuncture significantly increased levels of bifidobacteria and lactobacillus among thirty obese women; aside from achieving marked reductions in BMI and improving deficiencies in gut flora composition relative to controls, acupuncture reduced levels of pathogenic bacteroides, thought to promote obesity by causing the body to absorb and store more calories from food.[35] Given that alterations in bacteroides have been implicated in T1DM, Ulcerative Colitis and Crohn's Disease,[36,37,32] these preliminary findings suggest a novel application for acupuncture in treating gut dysbiosis in autoimmune disease.

Pain

As the analgesic effects of acupuncture have been previously described, this section will focus on aspects of pain germane to chronic illness, in particular the development of maladaptive pain perception and pain behaviors known to accompany the chronification of pain. Acupuncture has indicated a capacity for pain relief in numerous chronic pain conditions of non autoimmune origin, including low back pain, osteoarthritis, chronic headache, and shoulder pain,[38,39] as well as pain specific to autoimmune conditions, including Crohn's Disease, Lupus, and MS,[40,41,42] along with evidence from autoimmune animal models.[43,22] Given that co-morbidities such as insomnia, immunosuppression, eating disorders, cognitive deficits, impaired stress responses, and anxiety and depression are common among chronic pain patients, the importance of addressing not only pain itself but also its impact on quality of life and emotional/ affective states is of great importance.[44,45,46] Acupuncture has demonstrated effectiveness in modulating serotonin (5-HT) activity and expression, highlighting a potential avenue for the treatment of

both chronic pain and co-morbid mood disorders;[12,47,48] In a rat model of depression, a condition marked by reduced hippocampal release of 5-HT, acupuncture significantly increased 5-HT and mRNA expression of 5-HT relative to untreated controls,[12] while another rat model of depression illustrated significant behavioral change and restoration of the ratio between 5-HT and its metabolite 5-HIAA among acupuncture-treated rats relative to controls.[12,13,47]

In light of the knowledge that chronic pain has been shown to induce functional and structural shifts in areas of the brain involved in pain processing, pain memory, and pain behavior, as well as areas responsible for mediating reward and motivation, including the nucleus acumbens (NAc), ventral tegmental area (VTA), the prefrontal cortex (PFC), the periaquaductal gray area (PAG) and the amygdala,[44,49] a potential role for acupuncture in modulating brain plasticity has become a sought-after research topic. An fMRI study examined the effects of acupuncture on regions of the brain showing impairment owing to chronic osteoarthritis of the knee: the periaqueductal gray matter (PAG), medial frontal cortex (MFC), and bilateral hippocampus (Hpc) - areas involved with attention to pain, pain memory and avoidance learning, and emotional distress.[30] Study subjects (n=44) displayed higher PAG - Hpc connectivity at the outset of the study, a pattern associated with increased attention to pain, anxiety and nociceptive memory, and lower PAG - MFC connectivity, also linked to increased attention to pain, as well as low expectation for analgesia, and higher pain avoidance.[30] Acupuncture restored proper connectivity between the affected brain regions, such that PAG - Hpc connectivity was lowered and PAG - MFC connectivity was strengthened relative to sham acupuncture.[30] These results led to improved pain scores as measured by the KOOS sport index, an indicator of not only pain, but also functioning in daily living, functioning in sports and recreation, and knee-related quality of

life. As the PAG is considered a hub for development and solidification of pain memory, learning and behavior, these findings suggest that acupuncture may play a role in updating nociceptive memory, and rectifying maladaptive pain behaviors such as pain avoidance and attention to pain.

FMRI research serves as a promising vehicle for better understanding how acupuncture influences brain activity and by extension, the processing of pain and pain perception. To date, fMRI studies have illustrated a role for acupuncture in stimulating brain areas involved with the affective, sensory, cognitive, and inhibitory aspects of pain processing.[50] Of particular relevance to a chronic pain population is the demonstrated capacity for acupuncture to yield long-lasting effects, with repeated treatment inducing habituation effects in affected brain areas,[50] hinting at the potential for this ancient practice to modulate maladaptive brain function and structure to positively affect pain sensation and perception.

DISCUSSION

Admittedly, what is known about autoimmunity is vastly eclipsed by what is yet to be discovered; and to that end, one might posit that what is yet to be discovered is likely eclipsed by questions that are not yet even being asked. Several concepts, however, can be regarded with certainty, namely that autoimmunity involves both aberrant immune system activity that engenders chronic, self-perpetuating inflammatory responses, and an impaired stress response, owing to not only the pathological dysregulation of the HPA Axis but also to the inherently stressful nature of being chronically ill. Furthermore, research is increasingly supportive of the notion that gut dysbiosis and intestinal permeability play contributing roles in autoimmune pathogensis, and, while it manifests differently across autoimmune disorders, pain is a

sufficiently prominent feature to warrant its inclusion in this exploration of the use of acupuncture to treat autoimmune conditions.

The anti-inflammatory actions of acupuncture are of particular salience for the autoimmune disease population, given that inflammation is a hallmark feature of autoimmunity. Not only has acupuncture been shown to strengthen mediators of innate immunity,[18,20,51] the immune system's first line of defense, but it also has repeatedly demonstrated effectiveness in restoring balance to skewed T cell profiles[18,21,22,23,24,43] characteristic of autoimmune conditions. That acupuncture reduces inflammatory cytokines both systemically and locally in affected organs such as the lungs, liver, and intestines,[33] carries considerable implications for the autoimmune disease population, as it is not uncommon for autoimmune patients to seek out and receive acupuncture only once the disease has progressed - and inflammation has spread - significantly, surpassing the point during earlier stages of disease in which inflammation may be more localized and responsive to treatment. Moreover, research associating altered T cell activity with pain in autoimmune disease may lend further support for the inclusion of acupuncture in autoimmune disease treatment regimens; infiltration of T cells into the CNS has been linked to chronic pain, having been shown to induce thermal hyperalgesia and mechanical allodynia in rat models of pain as well as mouse models of the autoimmune conditions Multiple Sclerosis and Guillain-Barrée syndrome.[45] In light of the findings that passive transfer of Th1 cytokines induced pain hypersensitivity, while passive transfer of Th2 cytokines attenuated pain hypersensitivity in a study of neuropathic pain in rats,[45] one could posit that acupuncture's anti-inflammatory effects could serve the dual purpose of attenuating both pain and inflammation among sufferers of chronic pain conditions.

The overlap between immune function and stress is extensive; that stress alone can trigger an inflammatory cascade is a simple illustration of this point.[19] Importantly, while acute stressors have been shown in animal models to shift immune phenotypes from autoimmune disease susceptibility towards autoimmune disease resistance, chronic stress, on the other hand, hinders the body's ability to maintain resilience against disease.[52] Chronic stress has been shown to impair immune function by decreasing the proliferative capacity of lymphocytes, and reducing levels of circulating B cells and T cells - specifically helper T cells and cytotoxic T cells - leaving the body ill-equipped to fight off potential immune infection or insult.[53] Furthermore, chronic stress alters CORT release over time, allowing for unchecked proliferation of inflammatory cytokines, ultimately leading to heightened immune reactivity.[7] Chronic stress or, more specifically, HPA axis over-activation and subsequent HPA axis dysfunction, has been cited in a number of autoimmune conditions, including Crohn's Disease, Colitis, Rheumatoid Arthritis and Multiple Sclerosis, among others.[54] HPA axis dysfunction can lead to increased production of CORT, significant not only because elevations in CORT are associated with increases in pro-inflammatory cytokines, but also because excess CORT is known to decrease glucocorticoid receptor numbers and function, weakening the body's response to CORT's immunoregulatory actions.[28] This decreased responsiveness of glucocorticoid receptors to CORT is termed glucocorticoid (GC) resistance, which can amplify inflammatory responses and impair the HPA axis' regulatory effect on the immune system.[55,56] Acupuncture has been shown to increase protein expression of the glucocorticoid receptor (GR) in the hippocampus, pituitary and hypothalamus, promoting connectivity between the GR and CORT, thereby strengthening GR's

regulatory effects on the HPA axis, effectively attenuating elevated CORT production and reducing HPA axis hyperexcitation to affect an anti-stress response.[28]

Worth highlighting are the previously-mentioned studies in which acupuncture was shown to disrupt the stress response by blunting stress-induced elevations in CRH, ACTH, and CORT in mouse models of cold stress.[12,27] While the administration of acupuncture prior to stressful events, as in the case of the first study, evidently confers a protective advantage, it is not as clinically-applicable a scenario as the second study, in which acupuncture administered immediately after cold stress exposure achieved the same stress hormone preventing effects as the former study.[27] The HPA axis hormones in acupuncture-treated rats were unchanged by cold stress, remaining similar to that of un-stressed and un-treated controls for 4 days after acupuncture treatment had stopped, despite the continuation of cold stress exposure.[27] These long lasting effects are particularly enticing for patient populations predisposed to stress susceptibility, such as autoimmune disease patients. Moreover, on the behavioral front, depressive and anxious behavior was unseen in the acupuncture-treated rats, while stressed and un-treated rats displayed significant depressive and anxious behavior following stress exposure, again emphasizing the capacity for acupuncture to address not only physical but also psycho-emotional aspects of health.[27]

Alterations in gut flora composition and function, or more succinctly, ‘gut dysbiosis,’ have been associated with numerous disease states, including metabolic syndrome, obesity, diabetes, malignancy, and allergic conditions, as well as autoimmune disease, perhaps unsurprisingly, given that the microbiota serves as an important hub for immune system development and maintenance.[37,57] The microbiota play critical roles in bacterial recognition and

differentiation of Th cell subsets, influencing the production and proliferation of inflammatory and anti-inflammatory Th cells and their cytokines.[37] Pathogenic gut bacteria have been shown to promote the differentiation of Th cells into the inflammatory Th17 type over the anti-inflammatory, immune-suppressing Treg type; Th17 cells produce IL-17, which has been associated with the development of numerous autoimmune diseases and animal models of autoimmune disease, namely Crohn's Disease, Collagen Induced Arthritis (proxy for Rheumatoid Arthritis), Experimental Autoimmune Encephalitis (proxy for Multiple Sclerosis), and Non Obese Diabetes (proxy for T1DM), along with other inflammatory and allergic disorders.[25,26,37] That acupuncture demonstrated effectiveness in restoring balance to skewed Th17 to Treg ratios to affect a reduction in inflammation in both Crohn's Disease and an animal model of asthma posits a potential role for it in the treatment of other autoimmune conditions in which an imbalance between Th17 and Treg cytokine subsets is implicated.

Importantly, that pathogenic bacteria contribute to the development of disease does not suggest that an absence of bacteria is optimal; rather, animals raised in germ free (GF) conditions (or rendered germ free through dietary and pharmacological interventions) have impaired immune system development; of relevance to autoimmunity, GF animals display altered antibody production and T cell differentiation, potentiating the production of aberrant immune cell development and proliferation.[36] Increased prevalence of Type 1 Diabetes (T1DM) in countries with enhanced hygiene and sanitation practices, relative to less westernized neighboring nations. Supporting this observation is the increased prevalence of Type 1 Diabetes (T1DM) in countries with enhanced hygiene and sanitation practices, relative to less westernized neighboring nations. [36] Interestingly, the implantation of GF mice with a single species of commensal bacteria has

been shown to stimulate the production of Tregs, which produced IgE that yielded a protective effect from inflammatory colitis.[37] Though not pertaining to an outright disease state, the transfer of gut flora from both obese and lean hosts to GF mice has been to shown to lead to obesity among mice receiving microbes from obese volunteers, while mice receiving microbes from lean volunteers remained lean.[36,57,58] Furthermore, the microbiome has been shown to be influenced by stress and to itself influence behavior, as an animal model of chronic unpredictable stress demonstrated reductions in lactobacillus that induced despair behavior and was reversed by the administration of a lactobacillus-containing probiotic.[59] Other factors the have been shown to impact the microbiota include diet, medications, pregnancy (owing to the shift towards Th2 dominance), cesarean section vs vaginal delivery, and breastfeeding vs formula feeding.[8,36,37,57] Taken together, these findings illustrate the extent to which gut microbes can influence health and disease; though the research is not yet robust, the preliminary evidence of acupuncture's capacity to modulate the gut flora in favorable ways - increasing levels of beneficial bacteria and reducing levels of pathogenic bacteria - holds promise for patients affected by gut dysbiosis.

The second part of the altered gut homeostasis equation is Intestinal permeability, a breach of the wall that separates the gut from the rest of the body; when the epithelial tissue lining the gut suffers a loss of integrity and becomes permeable, food proteins travel into the bloodstream where the immune system may recognize them as foreign antigens and activate an immune response.[58,60] Intestinal permeability has been linked to multiple autoimmune diseases, including Ulcerative Colitis, Crohn's Disease, Celiac Disease, Ankylosing Spondylitis, Juvenille Onset Arthritis, Psoriatic Arthritis, Primary Biliary Cirrhosis, and Type 1 Diabetes.[58,60] The

impact of intestinal permeability on autoimmune pathogenesis, though not yet fully quantified or appreciated, is undoubtedly considerable, as it potentiates immune activation in response to food antigens, which, unless a patient is fasting, are regularly and frequently introduced into the body. Aside from its role in reducing inflammation and modulating gut flora to improve gut health and by extension, immune health, acupuncture has been shown to reduce intestinal permeability by increasing mRNA expression and enhancing structure and function of the tight junction proteins (TJP's) that regulate the gut barrier.[21,29,31,33] Additionally, acupuncture's proven capacity to activate enteric glial cells, also involved in preserving the integrity of the gut barrier through inhibition of transcription factor NF-κB, further supports its role in treating patients with intestinal permeability.[29]

The potential for acupuncture to influence chronic pain in autoimmunity is significant, owing not only to its well supported analgesic effects,[10,11,13,14,18,30,61] but also to its previously-described effects on reducing inflammation and restoring balance to skewed T cell ratios, modulating the stress response, restoring balance to dysbiotic gut flora profiles, and supporting the preservation of gut barrier integrity. Furthermore, fMRI research illustrating the capacity for acupuncture to modulate brain plasticity to affect not only pain sensation but also its accompanying maladaptive pain perceptions and behaviors is particularly compelling,[30,50] as is the research highlighting the role of acupuncture in improving functional capacity and quality of life among sufferers of chronic pain conditions, autoimmune or otherwise.[40,41,42,61] While acupuncture research has not yet investigated a potential role in mediating autoantibody activity, specifically autoantibody-induced pain, it is not unreasonable to expect that the weight of the

evidence of acupuncture's influence on immune function, the stress response, the microbiome, and pain are sufficiently convincing to warrant further exploration of this topic.

Acupuncture Limitations

No discussion of the merits of a given therapeutic intervention should be concluded without mention of its weaknesses. To that end, it should be summarily emphasized that acupuncture does not work for every patient,[10] and that the needs of chronically ill patients whose autoimmune disease severity has progressed to the extent of significantly hindering functional capacity and quality of life - preventing them from working, performing activities of daily living, maintaining social connection, and requiring extensive biomedical treatment regimens - may exceed the capacity for acupuncture to regenerate the body's own self-healing capacities. This is not to say that acupuncture could not confer some measure of palliative benefit but rather to stress this discussion does not intend to claim acupuncture as a miracle cure.

The validity of acupuncture's effects has historically been a divisive topic within the allopathic medical and research communities. A comprehensive exploration of the reasons for which acupuncture research has yielded mixed results is tangential to the focus of this paper and the project that informed it; however, it is important to highlight how the construct of acupuncture research may lead to inconclusive results so as to facilitate readers' understanding and contextualization of the results. Whereas a substantive body of evidence supports the role of acupuncture in yielding significant reductions in pain and equally valuable improvements in quality of life,[38,39,40,41] many systematic reviews and meta-analyses have been reticent to recommend acupuncture owing to limited effect sizes relative to sham control, inadequate blinding, lack of methodological uniformity across studies, and other factors. The use of poorly

constructed sham techniques of questionable viability contribute to the discord perhaps more than any other factor, as sham acupuncture is employed in heterogeneous ways, none of which are physiologically inert. Accordingly, sham acupuncture often demonstrates some measure of efficacy in benefiting the patient population being studied, which creates an obstacle to isolating and validating the effects of verum acupuncture. While a sham should be predicated on the knowledge of how sham controls are both physiologically similar to and disparate from the verum intervention, in reality acupuncture studies tend to utilize shams focused on what to mimic based on known similarities with verum acupuncture, essentially sidestepping a major potential confounding element.[62] Though knowledge of acupuncture - and by extension, sham acupuncture - mechanisms has grown exponentially in recent years, the tendency towards using shams that mimic acupuncture with no regard for what should be avoided indicates a significant gap in the understanding of sham acupuncture and therefore, the ability to construct a viable one. All of this begs the question: could acupuncture conclusively and reliably demonstrate efficacy within the biomedical research paradigm or would research efforts be better spent utilizing pragmatic trials that compare clinical acupuncture with standard of care clinical interventions? Though this type of construct would limit internal validity, the ostensible gains in external validity may be sufficiently meaningful to warrant such a shift in how acupuncture research is conducted. It is this investigator's belief that the latter format would encourage greater acceptance of the practice and therefore, increased utilization and increased potential benefit to patients, autoimmune or otherwise.

CONCLUSION

The anti-inflammatory, stress hormone modulating, gut barrier preserving, and analgesic effects of acupuncture are of obvious importance to a patient population that suffers the heavy physiologic, functional, social, and psychoemotional burden that autoimmune diseases impose. While the capstone project and this discussion that summarizes it have focused primarily on these main pillars of autoimmunity and the ways in which acupuncture addresses them, it is this investigator's inclination to posit that the clinically-meaningful value of this ancient practice results not only from quantifiable improvements in immune function, stress responses, and pain, but also the nuanced, qualitative factors that make life more livable for patients of chronic autoimmune disease: improved mood, motivation, and perception, and increased functional capacity. Collectively, the benefits that acupuncture has been shown to confer render it well suited to a patient population that is often misunderstood and marginalized, and therefore in greater need of individualized, holistic care.

ACKNOWLEDGEMENTS

I would like to thank Dr. Libby Bradshaw for her support and guidance, and unwavering belief that I could finish this project even when I felt most defeated. I would also like to thank my own personal support squad - my parents and my boyfriend - for the countless words of encouragement, for patiently lending an ear so I could pontificate on a puzzling topic, and for accepting the slightly crazier-than-normal version of Meghan who was present throughout this process. Lastly, I am thankful for both the PREP and NESA communities, not only for their welcoming and supportive attitudes, but also for challenging and inspiring me on a continual basis.

REFERENCES

1. Anaya, J. (2012). Common mechanisms of autoimmune diseases (the autoimmune tautology). Autoimmunity Reviews, 11(11), 781-784. doi:10.1016/j.autrev.2012.02.002
2. Agmon-Levin, N., Lian, Z., & Shoenfeld, Y. (2011). Explosion of autoimmune diseases and the mosaic of old and novel factors. Cellular and Molecular Immunology, 8(3), 189-192. doi: 10.1038/cmi.2010.70
3. Lerner, A., Jeremias, P., & Matthias, T. (2016). The World Incidence and Prevalence of Autoimmune Diseases is Increasing. International Journal of Celiac Disease, 3(4), 151-155. doi: 10.12691/ijcd-3-4-8
4. Autoimmune Statistics. (n.d.). Retrieved May 12, 2017, from https://www.aarda.org/autoimmune-information/autoimmune-statistics/
5. Manzel, A., Muller, D. N., Hafler, D. A., Erdman, S. E., Linker, R. A., & Kleinewietfeld, M. (2013). Role of "Western Diet" in Inflammatory Autoimmune Diseases. Current Allergy and Asthma Reports, 14(1). doi:10.1007/s11882-013-0404-6
6. Rahsepar, A. A., Tavallaie, S., Abdi, H., Zhao, B., Abbasi, P., Nemati, M., . . . Ferns, G. (2011). Effects of body acupuncture versus auricular acupuncture on anthropometric, lipid profile, inflammatory and immunologic markers: a randomized controlled trial study. Clinical Biochemistry, 44(13). doi:10.1016/j.clinbiochem.2011.08.388
7. Bolon, B. (2012). Cellular and Molecular Mechanisms of Autoimmune Disease. Toxicologic Pathology, 40(2), 216-229. doi:10.1177/0192623311428481
8. Anaya, J., Ramirez-Santana, C., Alzate, M. A., Molano-Gonzalez, N., & Rojas-Villarraga, A. (2016). The Autoimmune Ecology. Frontiers in Immunology, 7. doi:10.3389/fimmu.2016.00139
9. Rosenblum, M. D., Gratz, I. K., Paw, J. S., & Abbas, A. K. (2012). Treating Human Autoimmunity: Current Practice and Future Prospects. Science Translational Medicine, 4(125). doi:10.1126/scitranslmed.3003504
10. Carlsson, C. (2002). Acupuncture mechanisms for clinically relevant long-term effects - reconsideration and a hypothesis. Acupuncture in Medicine, 20(2-3), 82-99. doi:10.1136/aim.20.2-3.82
11. Cheng, K. J. (2014). Neurobiological Mechanisms of Acupuncture for Some Common Illnesses: A Clinician's Perspective. Journal of Acupuncture and Meridian Studies, 7(3), 105-114. doi:10.1016/j.jams.2013.07.008
12. Le, J., Yi, T., Qi, L., Li, J., Shao, L., & Dong, J. (2016). Electroacupuncture regulate hypothalamic–pituitary–adrenal axis and enhance hippocampal serotonin system in a rat model of depression. Neuroscience Letters, 615, 66-71. doi:10.1016/j.neulet.2016.01.004
13. Zhao, Z. (2008). Neural mechanism underlying acupuncture analgesia. Progress in Neurobiology, 85(4), 355-375. doi:10.1016/j.pneurobio.2008.05.004
14. Yu, J., Zeng, B., & Hsieh, C. (2013). Acupuncture Stimulation and Neuroendocrine Regulation. International Review of Neurobiology Neurobiology of Acupuncture, 125-140. doi: 10.1016/b978-0-12-411545-3.00006-7
15. Huang, W., Pach, D., Napadow, V., Park, K., Long, X., Neumann, J., . . . Witt, C. M. (2012). Characterizing Acupuncture Stimuli Using Brain Imaging with fMRI - A Systematic Review and Meta-Analysis of the Literature. PLoS ONE, 7(4). doi:10.1371/journal.pone.0032960

16. Mori, H., Nishijo, K., Kawamura, H., & Abo, T. (2002). Unique immunomodulation by electro-acupuncture in humans possibly via stimulation of the autonomic nervous system. Neuroscience Letters, 320(1-2), 21-24. doi:10.1016/s0304-3940(02)00012-5
17. Kong, J., Kaptchuk, T. J., Polich, G., Kirsch, I., Vangel, M., Zyloney, C., . . . Gollub, R. (2009). Expectancy and treatment interactions: A dissociation between acupuncture analgesia and expectancy evoked placebo analgesia. NeuroImage, 45(3), 940-949. doi:10.1016/j.neuroimage.2008.12.025
18. Kim, S. K., & Bae, H. (2010). Acupuncture and immune modulation. Autonomic Neuroscience, 157(1-2), 38-41. doi:10.1016/j.autneu.2010.03.010
19. Watanabe, M., Kainuma, E., & Tomiyama, C. (2015). Repetitive manual acupuncture increases markers of innate immunity in mice subjected to restraint stress. Acupuncture in Medicine, 33(4), 312-318. doi:10.1136/acupmed-2014-010660
20. Silva, M. D., Bobinski, F., Sato, K. L., Kolker, S. J., Sluka, K. A., & Santos, A. R. (2014). IL-10 Cytokine Released from M2 Macrophages Is Crucial for Analgesic and Anti-inflammatory Effects of Acupuncture in a Model of Inflammatory Muscle Pain. Molecular Neurobiology, 51(1), 19-31. doi:10.1007/s12035-014-8790-x
21. Du, M. (2013). Electroacupuncture improves gut barrier dysfunction in prolonged hemorrhagic shock rats through vagus anti-inflammatory mechanism. World Journal of Gastroenterology, 19(36), 5988. doi:10.3748/wjg.v19.i36.5988
22. Yim, Y., Lee, H., Hong, K., Kim, Y., Lee, B., Son, C., & Kim, J. (2007). Electro-Acupuncture at Acupoint ST36 Reduces Inflammation and Regulates Immune Activity in Collagen-Induced Arthritic Mice. Evidence-Based Complementary and Alternative Medicine, 4(1), 51-57. doi:10.1093/ecam/nel054
23. Carneiro, E., Xavier, R., Castro, M. P., Nascimento, C. O., & Silveira, V. (2010). Electroacupuncture promotes a decrease in inflammatory response associated with Th1/Th2 cytokines, nitric oxide and leukotriene B4 modulation in experimental asthma. Cytokine, 50(3), 335-340. doi:10.1016/j.cyto.2010.01.005
24. Carneiro, E., Xavier, R., Castro, M. P., Nascimento, C. O., & Silveira, V. (2010). Electroacupuncture promotes a decrease in inflammatory response associated with Th1/Th2 cytokines, nitric oxide and leukotriene B4 modulation in experimental asthma. Cytokine, 50(3), 335-340. doi:10.1016/j.cyto.2010.01.005
25. Zhao, C., Bao, C., Li, J., Zhu, Y., Wang, S., Yang, L., . . . Wu, H. (2015). Moxibustion and Acupuncture Ameliorate Crohn's Disease by Regulating the Balance between Th17 and Treg Cells in the Intestinal Mucosa. Evidence-Based Complementary and Alternative Medicine, 2015, 1-11. doi:10.1155/2015/938054
26. Wei, Y., Dong, M., Zhang, H., Lv, Y., Liu, J., Wei, K., . . . Dong, J. (2015). Acupuncture Attenuated Inflammation and Inhibited Th17 and Treg Activity in Experimental Asthma. Evidence-Based Complementary and Alternative Medicine, 2015, 1-8. doi:10.1155/2015/340126
27. Eshkevari, L., Mulroney, S. E., Egan, R., & Lao, L. (2015). Effects of Acupuncture, RU-486 on the Hypothalamic-Pituitary-Adrenal Axis in Chronically Stressed Adult Male Rats. Endocrinology, 156(10), 3649-3660. doi:10.1210/en.2015-1018
28. Wang, S., Zhang, J., & Qie, L. (2014). Acupuncture Relieves the Excessive Excitation of Hypothalamic-Pituitary-Adrenal Cortex Axis Function and Correlates with the Regulatory

Mechanism of GR, CRH, and ACTHR. Evidence-Based Complementary and Alternative Medicine, 2014, 1-9. doi:10.1155/2014/495379
29. Hu, S. (2015). Electroacupuncture activates enteric glial cells and protects the gut barrier in hemorrhaged rats. World Journal of Gastroenterology, 21(5), 1468. doi:10.3748/wjg.v21.i5.1468
30. Egorova, N., Gollub, R. L., & Kong, J. (2015). Repeated verum but not placebo acupuncture normalizes connectivity in brain regions dysregulated in chronic pain. NeuroImage: Clinical, 9, 430-435. doi:10.1016/j.nicl.2015.09.012
31. Shang, H. (2015). Moxibustion combined with acupuncture increases tight junction protein expression in Crohn's disease patients. World Journal of Gastroenterology, 21(16), 4986. doi: 10.3748/wjg.v21.i16.4986
32. Wang, X. (2012). Moxibustion inhibits interleukin-12 and tumor necrosis factor alpha and modulates intestinal flora in rat with ulcerative colitis. World Journal of Gastroenterology, 18(46), 6819. doi:10.3748/wjg.v18.i46.6819
33. Song, Q., Hu, S., Wang, H., Lv, Y., Shi, X., Sheng, Z., & Sheng, W. (2014). Electroacupuncturing At Zusanli Point (St36) Attenuates Pro-Inflammatory Cytokine Release And Organ Dysfunction By Activating Cholinergic Anti-Inflammatory Pathway In Rat With Endotoxin Challenge. African Journal of Traditional, Complementary and Alternative Medicines, 11(2), 469. doi:10.4314/ajtcam.v11i2.35
34. Cutolo, M., Capellino, S., & Straub, R. H. (2008). Chapter 2 Sex Hormones, the Immune System and Autoimmune Diseases. Handbook of Systemic Autoimmune Diseases Endocrine Manifestations of Systemic Autoimmune Diseases, 13-19. doi:10.1016/s1571-5078(07)00202-4
35. Xu, Z., Li, R., Zhu, C., & Li, M. (2012). Effect of acupuncture treatment for weight loss on gut flora in patients with simple obesity: Table 1. Acupuncture in Medicine, 31(1), 116-117. doi: 10.1136/acupmed-2012-010209
36. Burkett, P. R., Lee, Y., Peters, A., & Kuchroo, V. K. (2014). T Cells and their Subsets in Autoimmunity. The Autoimmune Diseases, 69-86. doi:10.1016/b978-0-12-384929-8.00006-x
37. Bach, J., & Perez-Arroyo, A. (2014). Microbiome and Autoimmunity. The Autoimmune Diseases, 329-340. doi:10.1016/b978-0-12-384929-8.00025-3
38. Vickers, A. J., & Linde, K. (2014). Acupuncture for Chronic Pain. Jama, 311(9), 955. doi: 10.1001/jama.2013.285478
39. Zeng, Y., & Chung, J. W. (2015). Acupuncture for chronic nonspecific low back pain: An overview of systematic reviews. European Journal of Integrative Medicine, 7(2), 94-107. doi: 10.1016/j.eujim.2014.11.001
40. Bao, C. (2014). Randomized controlled trial: Moxibustion and acupuncture for the treatment of Crohn's disease. World Journal of Gastroenterology, 20(31), 11000. doi:10.3748/ wjg.v20.i31.11000
41. Greco, C. M., Nakajima, C., & Manzi, S. (2013). Updated Review of Complementary and Alternative Medicine Treatments for Systemic Lupus Erythematosus. Current Rheumatology Reports, 15(11). doi:10.1007/s11926-013-0378-3
42. Quispe-Cabanillas, J. G., Damasceno, A., Glehn, F. V., Brandão, C. O., Damasceno, B. P., Silveira, W. D., & Santos, L. M. (2012). Impact of electroacupuncture on quality of life for patients with Relapsing-Remitting Multiple Sclerosis under treatment with immunomodulators:

A randomized study. BMC Complementary and Alternative Medicine, 12(1). doi: 10.1186/1472-6882-12-209
43. Liu, Y., Liu, X., Bai, S., Mu, L., Kong, Q., Sun, B., . . . Li, H. (2010). The effect of electroacupuncture on T cell responses in rats with experimental autoimmune encephalitis. Journal of Neuroimmunology, 220(1-2), 25-33. doi:10.1016/j.jneuroim.2009.12.005
44. Modulation of Pain, Nociception, and Analgesia by the Brain Reward Center
45. Mifflin, K. A., & Kerr, B. J. (2016). Pain in autoimmune disorders. Journal of Neuroscience Research, 95(6), 1282-1294. doi:10.1002/jnr.23844
46. Goebel, A. (2016). Autoantibody pain. Autoimmunity Reviews, 15(6), 552-557. doi:10.1016/j.autrev.2016.02.011
47. Pilkington, K. (2013). Acupuncture Therapy for Psychiatric Illness. International Review of Neurobiology Neurobiology of Acupuncture, 197-216. doi:10.1016/b978-0-12-411545-3.00010-9
48. Viguier, F., Michot, B., Hamon, M., & Bourgoin, S. (2013). Multiple roles of serotonin in pain control mechanisms —Implications of 5-HT7 and other 5-HT receptor types. European Journal of Pharmacology, 716(1-3), 8-16. doi:10.1016/j.ejphar.2013.01.074
49. Yu, R., Gollub, R. L., Spaeth, R., Napadow, V., Wasan, A., & Kong, J. (2014). Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. NeuroImage: Clinical, 6, 100-108. doi:10.1016/j.nicl.2014.08.019
50. Hammer, A., Jansma, B. M., Tempelmann, C., & Münte, T. F. (2011). Neural Mechanisms of Anaphoric Reference Revealed by fMRI. Frontiers in Psychology, 2. doi:10.3389/fpsyg.2011.00032
51. Yamaguchi, N., Takahashi, T., Sakuma, M., Sugita, T., Uchikawa, K., Sakaihara, S., . . . Kawakita, K. (2007). Acupuncture Regulates Leukocyte Subpopulations in Human Peripheral Blood. Evidence-Based Complementary and Alternative Medicine, 4(4), 447-453. doi:10.1093/ecam/nel107
52. Stojanovich, L. (2010). Stress and autoimmunity. Autoimmunity Reviews, 9(5). doi:10.1016/j.autrev.2009.11.014
53. Mizokami, T., Li, A. W., El-Kaissi, S., & Wall, J. R. (2004). Stress and Thyroid Autoimmunity. Thyroid, 14(12), 1047-1055. doi:10.1089/thy.2004.14.1047
54. Silverman, M. N., & Sternberg, E. M. (2012). Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Annals of the New York Academy of Sciences, 1261(1), 55-63. doi:10.1111/j.1749-6632.2012.06633.x
55. Mitsonis, C. I., Zervas, I. M., Mitropoulos, P. A., Dimopoulos, N. P., Soldatos, C. R., Potagas, C. M., & Sfagos, C. A. (2008). The impact of stressful life events on risk of relapse in women with multiple sclerosis: A prospective study. European Psychiatry, 23(7), 497-504. doi:10.1016/j.eurpsy.2008.06.003
56. Sorrells, S. F., Caso, J. R., Munhoz, C. D., & Sapolsky, R. M. (2009). The Stressed CNS: When Glucocorticoids Aggravate Inflammation. Neuron, 64(1), 33-39. doi:10.1016/j.neuron.2009.09.032
57. Shamriz, O., Mizrahi, H., Werbner, M., Shoenfeld, Y., Avni, O., & Koren, O. (2016). Microbiota at the crossroads of autoimmunity. Autoimmunity Reviews, 15(9), 859-869. doi:10.1016/j.autrev.2016.07.012

58. Daft, J. G., & Lorenz, R. G. (2015). Role of the gastrointestinal ecosystem in the development of type 1 diabetes. Pediatric Diabetes, 16(6), 407-418. doi:10.1111/pedi.12282
59. Marin, I. A., Goertz, J. E., Ren, T., Rich, S. S., Onengut-Gumuscu, S., Farber, E., . . . Gaultier, A. (2017). Microbiota alteration is associated with the development of stress-induced despair behavior. Scientific Reports, 7, 43859. doi:10.1038/srep43859
60. Lerner, A., & Matthias, T. (2015). Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. Autoimmunity Reviews, 14(6), 479-489. doi:10.1016/j.autrev.2015.01.009
61. Wang, L., Zhang, Y., Dai, J., Yang, J., & Gang, S. (2006). Electroacupuncture (EA) modulates the expression of NMDA receptors in primary sensory neurons in relation to hyperalgesia in rats. Brain Research, 1120(1), 46-53. doi:10.1016/j.brainres.2006.08.077
62. Langevin, H. M., Wayne, P. M., Macpherson, H., Schnyer, R., Milley, R. M., Napadow, V., . . . Hammerschlag, R. (2011). Paradoxes in Acupuncture Research: Strategies for Moving Forward. Evidence-Based Complementary and Alternative Medicine, 2011, 1-11. doi: 10.1155/2011/180805