Acupuncture for Posttraumatic Stress Disorder: Conceptual, Clinical, and Biological Data Support Further Research

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SUMMARY

Posttraumatic stress disorder (PTSD) is common, debilitating, and has highly heterogeneous clinical and biological features. With the exception of one published preliminary clinical trial, rationale in support of the efficacy of acupuncture, a modality of Chinese medicine (CM), for PTSD has not been well described. This is a focused review of conceptual and clinical features of PTSD shared by modern western medicine (MWM) and CM, and of biological mechanisms of acupuncture that parallel known PTSD pathology. MWM and CM both recognize individual developmental variables and interactions between external conditions and internal responses in the genesis of PTSD. There is one published and one unpublished clinical trial that preliminarily support the efficacy of acupuncture for PTSD. Although there have been no mechanistic studies of acupuncture in human PTSD, extant research shows that acupuncture has biological effects that are relevant to PTSD pathology. Conceptual, clinical, and biological data support possible efficacy of acupuncture for PTSD. However, further definitive research about simultaneous clinical and biological effects is needed to support the use of acupuncture for PTSD in health care systems.

Introduction

Posttraumatic Stress Disorder (PTSD) is a common and complex illness with high psychiatric and medical comorbidity and impairment in daily functioning. Interventions for PTSD are similarly varied and have complex mechanisms of action. There is preliminary evidence that acupuncture may be an efficacious, safe, and acceptable treatment for PTSD. Efficacy may be due to similarities between the known pathology of PTSD and mechanisms of action of acupuncture. The stage is set in this article by reviewing the known epidemiology and pathology of PTSD from a modern western medicine (MWM) perspective, which is then compared and contrasted with a Chinese medicine (CM) perspective. Given the wealth of knowledge about PTSD, this review only summarizes major findings. Effective treatments are then reviewed. Finally, data are presented showing that acupuncture has effects in biological systems that are relevant to PTSD. This is not a comprehensive review of PTSD pathology or mechanisms of acupuncture, nor is the intent to contrast acupuncture with other interventions or offer “relative worth” of established interventions. Rather, this review summarizes the potential value of and need for further research about acupuncture for PTSD.

Two Perspectives on the Genesis of PTSD

MWM's Understanding of PTSD

PTSD is characterized by reexperiencing aspects of the original trauma, avoidance and numbing of trauma reminders, and general hyperarousal [1,2]. Cognitive, emotional, and somatic symptoms other than those defined in the DSM-IV also occur in PTSD sufferers [3]. Lifetime prevalence of PTSD in community samples is around 6.8% [4] and as high as 30% among Vietnam veterans [5] and female victims of rape [6]. Recent Iraq and Afghanistan war veterans have 13–16% PTSD prevalence, dependent on the degree of combat exposure [7]. The estimated cost for mental health-related expenses in these veterans is \$4–6 billion over 2 years [8]. PTSD is heterogeneous by individual variables and developmental period during which it emerges, by supposed causal events (trauma exposure), and by the complexity of its comorbidity and known pathology.

Individual Variables

What an individual “has” or “brings to” a traumatic experience are critical determinants of whether or not PTSD will develop.

As examples, there are genetic [9], morphologic [10], and social determinants (such as gender, age, and socioeconomic status) of PTSD [11]. These determinants are interactive. For example, the social context in which a primate is reared is a determinant of long-term morphological changes in stress-sensitive brain areas [12].

Unfortunately, young children and adolescents are exposed to various traumata. The risk of developing PTSD likely varies by trauma type, age of exposure, and moderating environmental and genetic variables. It has become clear that trauma exposure during early development is a significant risk factor for altered biology, stress reactivity, and later medical and psychiatric illness [13–15]. It is unclear if there are developmental periods during which trauma exposure is more likely to lead to PTSD than other periods.

Supposed Causal Events

Common events that comprise traumatic exposure include motor vehicle accidents, natural and human-caused disasters, childhood abuse and neglect, interpersonal violence, tragic death of a loved one, witnessing of violence, and war-related events. Approximately 60% of men and 51% of women in the United States report exposure to one or more traumatic event [4]. Trauma exposure coupled with a host response involving intense fear, helplessness, or horror comprises the first, or “A,” criterion of PTSD [1], and is by definition necessary but not sufficient for developing PTSD [16]. Perceptions of threat and psychological preparedness also mediate the association of traumatic experience with PTSD [17,18]. Trauma exposure alone is a risk factor for developing distressing symptoms, severe medical/psychiatric illness, poor health habits, and decreased life expectancy [19–25]. The risk of developing PTSD after trauma exposure varies by type of exposure [6,26].

Comorbidity

PTSD is highly comorbid (83–90%) with other psychiatric disorders, including mood, substance use, personality, and panic disorder [27]. Approximately 50% to 60% of PTSD patients have major depressive disorder (MDD) [27]. Among veterans with PTSD in primary care, 87% have one or more comorbid psychiatric disorder, the most common being depression [28]. Both self-reported cardiovascular symptoms [29–33] and objectively assessed cardiovascular diseases [34–37] are more prevalent in PTSD patients than in community samples [38]. There is also a higher prevalence of self-reported arthritis, hypertension and autoimmune diseases [39], diagnosed rheumatoid arthritis, psoriasis or other autoimmune diseases [40,41], and diagnosed fibromyalgia and irritable bowel disease [31] in PTSD compared to control subjects. Diabetes mellitus is more prevalent in PTSD patients (15%) compared to those with trauma but no PTSD (9%) and to those with no trauma (6%) [42].

Known Pathology

Phenomenologically, stress exposure coupled with a host response of severe fear and/or helplessness defines psychological trauma, which is the manifestation of gene–environment interactions critical for the genesis of PTSD. Clinicians often observe that it is as if the PTSD sufferer is “stuck” in the “freeze” response, unable to successfully process the event by fighting or fleeing danger. Thus, perceived threat continues even when the acute danger is no longer present, and stimuli that are reminiscent of those that occurred during the trauma (triggers) continue to provoke fear and alarm. This state of a frozen stress response, or the failure of processing a traumatic experience, involves multiple biological systems. The known pathology of PTSD thus parallels its complex clinical comorbidity. For example, neurological mechanisms of PTSD, depression, and other anxiety disorders have many similarities [43,44], and the known genetic variance for depression and other anxiety disorders accounts for the majority of known genetic variance for PTSD [45]. Major summative findings to date indicate a complex pathological state that includes alterations in central nervous system (CNS) processes that influence cognition, emotion, and somatic functioning, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and autonomic nervous system (ANS) dysfunction. Recent work has identified a low-level proinflammatory state in PTSD that may be a mediator of the increased risk for medical illness. There is also a burgeoning literature about the genetics of PTSD that points to polygenetic and gene expression control.

The CNS

An expert review identifies the complex and heterogeneous neurological response to symptom provocation in PTSD [46]. Substantial corroborative data implicate the medial prefrontal cortex (mPFC) and amygdala as being critically involved in PTSD: many neuroimaging studies show increased amygdala reactivity—mostly right sided [47]—and a failure of mPFC and anterior cingulate cortex (ACC) activation during traumatic reexperiencing [48]. These interconnected functions are thought to be the neural correlate of the failure of recovery of the stress response that is central to PTSD. The mPFC is also implicated in emotional and cognitive interactions involved in fear conditioning, habituation, and endocrine responses relevant to PTSD [49,50]. However, these functions are complex. For example, a recent study concluded that focal damage to the amygdala or the ventromedial PFC appears protective against the development of PTSD [51], contrary to expectations that such lesions would confer an increased risk due to loss of fear-controlling inhibitory actions on the amygdala. Other brain areas are involved in PTSD, such as the subcallosal cortex, rostral and caudal ACC, hippocampus, hypothalamus, insula, and other frontal nuclei, which are integral parts of the limbic system involved in regulating the HPA axis and the ANS.

The HPA Axis

Essential HPA disturbances in PTSD are low cortisol signaling, increased responsiveness of glucocorticoid receptors, enhanced

release of hypothalamic corticotropin-releasing hormone (CRH), and enhanced cortisol negative-feedback inhibition [52]. The most consistent finding in chronic PTSD is increased CRH [53,54] and diminished peripheral activity reflected by low serum or urinary cortisol output [55–60]. Some studies about cortisol levels or diurnal variability are conflicting [61], yet when PTSD is severe and chronic, relative hypocortisolemia is usual and one of the most consistent findings.

The ANS

Disturbances of both resting ANS tone and ANS stress-reactivity in PTSD are well established [62–65], although ANS stress-reactivity to trauma-related stressors is more pathognomonic than ANS tonal disturbances [66]. Research has consistently shown phasic activation of sympathetic nervous system (SNS) functions in PTSD in response to trauma-related stimuli, where generic stressors do not reliably activate the SNS [67,68]. Compared to controls, patients with PTSD most consistently show increased central norepinephrine levels [69], and increased output of urinary catecholamines (CATS) [55,70,71], although a few studies are contradictory [69,72]. There are only a few published reports of parasympathetic nervous system activity in PTSD. They have shown a significantly lower resting respiratory sinus arrhythmia (the amplitude of rhythmic fluctuations in heart rate associated with breathing) in PTSD than in controls, the absence of an expected heart rate variability response to trauma recall in PTSD subjects [73,74], and a low respiratory sinus arrhythmia during exposure to trauma-related stimuli [75].

Inflammation

The medical comorbidity associated with PTSD may be mediated by disinhibition of inflammatory mediators. This view is consistent with the fact that CNS regulation of the HPA axis and ANS seen in PTSD is compatible with inflammatory disinhibition. While there have been conflicting findings about immune cell number and function in PTSD [61], studies are more consistent in finding an increase in the concentration of proinflammatory mediators—such as C-reactive protein, interleukins (IL) IL-1, IL-1 β , and IL-6, and tumor necrosis factor-alpha (TNF- α) [76–78]—that are recognized to accelerate atherosclerosis [79], encourage insulin resistance [80], and alter pain responsiveness [81]. Recent work by von Kanel and colleagues corroborates evidence for low-grade chronic inflammation in PTSD, even when controlling for traditional cardiovascular risk factors [82]. TNF- α was higher in PTSD patients than in controls, and there was a trend toward higher IL-1 β in PTSD patients. After controlling for medical and psychiatric correlates of inflammatory markers, IL-4 was lower in PTSD patients and TNF- α and IL-1 β became less significant. The investigators computed one net score of proinflammatory activity, which was significantly correlated with frequency, intensity, and total frequency and intensity scores of all three symptom clusters and total PTSD symptoms. Other investigators have also found that severity and chronicity of PTSD are associated with alterations in inflammatory markers [78].

Genetics

Twin studies provide the best evidence that PTSD is heritable [52,83]. Genome-wide association studies have not been conducted for PTSD [84]. Ten case-control candidate gene association studies have been published, showing promise for three genes as part of PTSD pathology: dopamine receptor D2, dopamine transporter, and serotonin transporter [85–94]. Four gene expression analysis studies have been published. The first in acute PTSD used the semiquantitative microarray or “gene chip” method to measure broad-scale gene expression in peripheral blood cells of trauma survivors acutely and 1 and 4 months later [95]. Transcriptional signatures distinguished PTSD from non-PTSD subjects at each time point, despite similar levels of trauma. Three more recent studies using quantitative reverse-transcription polymerase chain reaction analysis have identified eight genes that are differentially expressed in PTSD compared to trauma-exposed controls: IL-18 ($P = 0.005$), IL-16 ($P = 0.041$), thioredoxin reductase ($P = 0.027$), superoxide dismutase 1 ($P = 0.016$), endothelial differentiation sphingolipid G-protein-coupled receptor 1 ($P = 0.038$), cystine/glutamate antiporter Xc(-) ($P = 0.049$), p-11, and FK506-binding protein 5 [96–98].

The CM and Acupuncture Perspective

CM includes many theoretical perspectives and resultant types of interventions, such as herbal treatment, moxibustion, cupping, and acupuncture, which may be used as monotherapies or combined to treat complicated patterns of illness. This may be thought of as similar to utilizing medication and psychotherapy for patterns of illness in MWM. For example, uncomplicated obsessive-compulsive disorder (OCD) may be successfully treated with psychotherapy alone, where refractory OCD with comorbid depression almost always requires both medication and psychotherapy to be successful [99]. Similarly, the treatment of PTSD depends on comorbidity and symptom structure [99]. Acupuncture itself is a heterogeneous group of therapies [100] where solid needles are placed into rationally chosen points in subcutaneous tissue for a given period of time and are manipulated to obtain the sensation of “de qi” (a fullness or heaviness and warmth but not pain) in order to move vital energy around the body to restore balance between body systems.

Individual Variables

As in MWM, CM recognizes individual variables as crucial determinants of illness. As further detailed below, all individuals are reflections of their external, natural world. One theoretical branch of CM posits that all living things are made up of five primary elements—water, wood, fire, earth, and metal—which are each related to external seasons and to internal organ systems. Just as winter precedes and gives rise to spring, water precedes and gives rise to wood, and the kidney/bladder system provides nurturing and control on the liver/gallbladder system. Just as a harsh winter begets a spring that is different than one that follow a mild winter, so too the balance between internal organ systems varies dependent on the timing and nature of one’s birth and the

conditions that occur during one's development. The ongoing balance, or imbalance, between these systems becomes a hard-wired part of the person over time, and is referred to as one's constitution. In CM, the constitution is sometimes referred to as the "root" that predisposes an individual to illness, and is similar to the way MWM considers genetics, and more recently gene-early environment interactions as predisposing individuals to disease.

Supposed Causal Events

Similarly, CM recognizes that both external and internal conditions/events may be pathogenic to illness. Common external conditions thought to promote imbalances in the functioning of the five elements include wind, heat, cold, dampness, and dryness, highlighting the internal connection to nature. Common internal conditions that promote imbalance and illness include joy, sympathy, worry, grief and sadness, fear, and anger. Trauma exposure in CM might best be thought of as an internal event (e.g., fear and worry) in reaction to the environment, where the five elements may be acutely imbalanced due to system shock. This parallels MWM thinking about the genesis of PTSD. Unlike MWM, the natural conditions in which the exposure occurs (e.g., cold, damp) is a more important determinant of pathogenesis. However, MWM certainly recognizes that external conditions may be important determinants of pathogenesis (e.g., dryness in dermatitis).

Comorbidity and Pathology

In mind-body dualistic terms, CM and particularly acupuncture might be thought of as primarily a somatic and not a psychological intervention. However, in the monistic CM tradition this dualism does not make sense since all five elements and their correspond-

ing body systems are highly interactive. Thus, acupuncture purports to work on both emotional and somatic symptoms. Comorbidity may be best thought of as having multiple patterns of disease based on imbalances between the five elements coupled with the supposed cause of illness rather than a combination of mental and physical symptoms. Treatment of emotional symptoms has been noted in CM as early as the third century in the Han Lun [101]. And, while it is clear that mental symptoms have been treated in China for approximately 3000 years [102,103], PTSD has not been a diagnostic entity in CM because of its different classification system and its relatively less focus on the brain. Because illness may arise from imbalances between the five elements, promoted by external or internal pathogenic factors in the context of a person's specific constitution, two people with similar symptoms may have different diagnosed patterns and syndromes, which provides a challenge to developing a standard CM diagnostic and treatment plan for a defined MWM illness. There is a paucity of research about what comprises PTSD from a CM perspective, and what the comorbid CM patterns are.

One published study describes CM diagnostic patterns and subsequent treatment planning for PTSD [104]. These were determined by conducting: (1) a textbook review of the potential CM diagnoses and points to use for symptoms of PTSD, (2) a survey of 20 CM experts to obtain opinions about diagnoses and points to use, and (3) comparative pilot diagnosis and treatment planning with 22 PTSD subjects. As can be seen in Table 1, the primary disease patterns observed according to CM principles were Heart Shen disturbances, Liver Qi (energy) stagnation, and deficiency in the Kidney system, which are more completely described in the published report [104]. Reflecting the disparate patterns identified in the textbook review and the survey of experts, there are many possible secondary patterns from which to choose points in a treatment plan. This finding of multiple possible CM diagnostic patterns

Table 1 Traditional Chinese Medicine (CM) diagnoses and acupuncture treatment protocol for PTSD (from Hollifield, 2007). All subjects were treated with points from the primary patterns. At each visit, up to three secondary points could be used in addition, and these could vary due to updated CM diagnostics

Primary patterns for standard protocol points	Grounding points/qi and blood deficiency Primary diagnostic patterns		Front points	Back points
			(bilateral)	(bilateral)
Primary patterns for standard protocol points	Grounding points/qi and blood deficiency Primary diagnostic patterns	Heart Shen disturbances	ST 36, SP 6	BL 20, BL 21
		Liver qi stagnation	HT 7, PC 6, Yintang	BL 14, BL 15
		Kidney deficiency	LR 3, (PC 6)	GB 20, BL 18
Secondary patterns for flexibly prescribed points	Secondary diagnostic patterns	Liver overacting on spleen	LR 13	BL 23
		Liver overacting on stomach	LR 14	(BL 18), (BL 20)
		Stomach fire	ST 44	(BL 18), (BL 21)
		Liver fire	LR 2	GV 14, (BL 21)
		Phlegm heat	ST 40	(GV 14), (BL 18)
		Phlegm damp	SP 9	(BL 20)
		Heart Yin/blood deficiency	HT 6	(BL 17), (BL 15)
		Spleen qi/Yang Deficiency	SP 3	(BL 20), (BL 23)
		Kidney Yin/essence deficiency	KI 6	BL 52, (BL 23)
		Kidney Yang/qi deficiency	KI 7	GV 4, (BL 23)
		Liver Yin/blood deficiency	LR 8	(BL 17), (BL 18)
		Stomach Yin deficiency	(ST 44)	(BL 21)

Points within brackets "()" are duplicate points.

in subjects with PTSD may be analogous to the multiple psychiatric and medical comorbidities found in MWM research. What has yet to be discovered is the relationship between biomedically defined pathology and CM diagnostic pathology.

Interventions for PTSD

In both MWM and CM, the goal of treatment is stabilization and reversal of pathology. Interventions that have evidence of efficacy for PTSD include a group of therapies under the rubric of cognitive behavior therapy (CBT) [105], eye movement desensitization and reprocessing [27], imagery rehearsal therapy (IRT) [106], and various pharmacological therapies as monotherapy or combined with CBT [99]. CBT is the most widely studied and accepted therapy. Trauma-focused CBT such as prolonged exposure and cognitive reprocessing provides large treatment effects (Cohen's $d = 1.0$ to 1.6) and is reported to be superior to therapies that do not focus on trauma [105,107–109]. However, trauma-focused CBT has its limitations, such as nonengagement in treatment and high withdrawal rates [109–112], and potentially a higher risk of becoming more symptomatic [113]. Moreover, a large percentage of people with PTSD, including veterans, may not want to engage in trauma-focused therapy in clinical practice [114–116]. Interventions that minimize exposure to trauma content such as IRT and stress inoculation training also have evidence of efficacy with large treatment effects [106,108,117]. There are a number of other emerging pharmacological and psychological therapies for PTSD that have preliminary evidence of efficacy [118]. The Institute of Medicine issued a report in 2007 that identified 2800 abstracts and 90 randomized clinical trials (53 psychotherapy and 37 pharmacotherapy) that met criteria for review and concluded that only the exposure therapy variant of CBT had sufficient evidence for proof of efficacy for PTSD [119], perhaps because of methodological limitations in the design of many studies.

Acupuncture for PTSD

The Clinical Approach

In the same study that identified CM diagnostic patterns and treatment planning for PTSD, a preliminary clinical trial evaluating a manualized verum acupuncture intervention was conducted [120]. To conserve the integrity of best practices in CM in the context of biomedical research, the study protocol included primary standard prescription points for all subjects—based on the primary disease patterns—and flexibly prescribed points to address secondary diagnostic patterns. As shown in Table 1, the standard point prescription alternated between front and back treatments: the front using 11 needles, and the back using 14 needles. There were 15 other points from which 0 to 3 flexibly prescribed points could be added at each session. Different needling techniques for standard points could also be utilized to address a participant's specific diagnosis or constitution. Individual treatment sessions were conducted for 1 h twice per week for 12 weeks, and included a standard CM interview about symptoms, pulse and tongue evaluation, and needle insertion, manipulation, and retention.

This acupuncture intervention was compared to group CBT and to a wait-list control (WLC), and showed a significant treatment effect for acupuncture, similar to CBT [120]. In summary, an intention-to-treat repeated-measures MANOVA and simple effects analyses showed that PTSD symptoms declined significantly from pre- to posttreatment for both acupuncture (Cohen's $d = 1.26$) and CBT ($d = 1.41$) but not for WLC ($d = 0.25$). Furthermore, 63% of those treated with acupuncture no longer met DSM-IV diagnostic criteria for PTSD at posttreatment. Reductions of PTSD symptoms and loss of diagnosis were maintained 3 months after treatment. Treatment effects on depression, anxiety, and impairment were similar to effects for PTSD. One subsequent study of acupuncture in military personnel, pending publication, has shown similar reductions in PTSD symptoms compared to a WLC group [121].

Just as in MWM interventions, there is significant individual variability in response to acupuncture. Gender may be one factor associated with differential effects. The limbic-paralimbic-neocortical network shows gender differences when mediating emotional and cognitive tasks during functional magnetic resonance imaging (fMRI), and there is deactivation of these networks during needle manipulation of acupuncture that are more extensive in females than in males [122]. In a study evaluating changes in electrical sensory thresholds and electrical pain thresholds after low-frequency electroacupuncture in healthy volunteers, there was an altered sensory threshold in men but not in women, the assessed pain threshold was increased in women and unchanged in men, and individual variation was larger in women than in men [123].

Acupuncture Has Effects in Systems Relevant to PTSD Pathology

There are no studies about biological effects of acupuncture in human PTSD. However, there is a large human and animal literature that shows biological effects of acupuncture in systems that parallel known PTSD pathology. In addition to clinical data provided above, these data are instructive as to why acupuncture may be efficacious for PTSD.

CNS and other Neural Pathways

Neural pathways are most likely the systems primarily affected with acupuncture. Effective acupuncture, which may require the sensation of "de qi" [124], stimulates A-delta fibers in the skin or muscle, which terminate in laminae I and V of the spinal cord. As seen in Figure 1, marginal cells (M) in the spinal cord project to somatosensory cortex via spinothalamic tracts; stalked cells (St) are responsible for enkephalin-induced segmental analgesia; and projections to the mPFC travel by spinoreticular tracts, reticular formation, and thalamus. Lamina I also projects to the locus coeruleus (LC) [125], the adrenergic control center of the brain. In addition, downward projections via the frontoarcuate connection to the hypothalamus extend to the descending inhibitory pathways directly to the LC and to serotonin and noradrenergic systems. Acupuncture causes a broad matrix of CNS response involving the mPFC, ACC, amygdala, hippocampus, hypothalamus,

Figure 1 General neural mechanisms of acupuncture (from Filshie et al., 1998) [160], reprinted with permission.

cerebellum, basal ganglia, and insula, assessed by multiple imaging techniques [126,127]. In both animals and humans, the response in various CNS targets are dependent on acupuncture type and frequency of stimulation [127–129]. Most relevant to PTSD, acupuncture may downregulate limbic functions in a coordinated fashion [128]. The literature is replete with data about specific and broader, orchestrated effects of either manual acupuncture (MA) or electroacupuncture (EA) on peripheral autonomic, immune and inflammatory, and genetic expression via neural and protein messengers. The review below is not an exhaustive one:

key studies are reviewed to indicate how acupuncture may affect known PTSD pathology.

The HPA Axis

Acupuncture has been found to have broad effects on HPA and ANS functions regulating blood pressure [130]. Studies in humans have assessed the effects of acupuncture on peripheral cortisol levels, which would be expected to change in different directions dependent on the clinical condition and the acupuncture

technique used. Compared to sham (placebo) acupuncture, EA reduced pain and plasma cortisol after 10 daily treatments in patients with knee osteoarthritis [131]. Similarly, compared to control groups, acupuncture changed plasma cortisol levels in women undergoing *in vitro* fertilization [132], in epilepsy patients similar to the medication Valpromide [133], in patients with irritable bowel disease [134], and in depression [135]. In the depression study, cortisol was decreased with acupuncture similar to with the medication maprotiline and to normal levels seen in nondepressed controls.

The ANS

Acupuncture is generally sympathoinhibitory in nonhuman animals [136], although EA may cause either excitation or inhibition of the sympathoadrenal medullary reflex depending on EA location [137]. EA may alter ANS function through multiple neurotransmitter systems relevant to PTSD in an opioid-dependent manner [138,139]. Acupuncture is also generally sympathoinhibitory in humans, and may have both reflexive and direct effects on the ANS and indirect effects via opioid (and perhaps other) systems. Acupuncture attenuates the blood pressure increase normally seen during mental stress [136], and coactivates cardiac vagal and muscle sympathetic nerves, depending on needle location and type of acupuncture [140–142]. Studies in animal models of tachycardia [143] and depression [144] have found changes in the expected direction of central and peripheral monoamine transmitters. Interestingly, in the tachycardia study, EA at a point used in the above-referenced acupuncture for PTSD study was shown to reduce heart rate and plasma CATS, but EA at a point not used in the PTSD study did not change CATS levels. Three human studies showed a change in serum CATS with acupuncture therapy. One compared EA with the medication Nicardipine and found that both decreased systolic and diastolic blood pressure and CATS [145]. One compared MA to the medication fluoxetine for postmenopausal symptoms and found that CATS changed with both interventions similarly [144]. The third found that EA plus psychotherapy compared to psychotherapy alone in anxiety from internet addiction was more clinically effective and was associated with a greater reduction of CATS [146].

Inflammation

Animal model studies have shown that acupuncture alters inflammatory markers that are relevant to PTSD, although the disease models were markedly different than PTSD. Markers most likely to be altered with acupuncture were reductions of proinflammatory cytokines IL-4 and IL-6 with EA in rats induced with ulcerative colitis [147], reductions of both plasma and cerebral IL-1 β and TNF- α with scalp acupuncture in rats induced with cerebral ischemia [148], reductions of IL-1 β and TNF- α and mRNA expression of genes regulating these cytokines in toe tissue with EA pretreatment of carrageenan-induced inflammation [149], and reductions in the levels of IL-1 β and TNF- α in joint synovial fluid in rabbits induced with knee osteoarthritis [150]. In depressed humans, EA and the medication fluoxetine reduced serum levels of the proinflammatory cytokine IL-1 β and restored the hypothesized imbalance between T-helper 1 and 2 functions by increas-

ing TNF- α and decreasing IL-4 in responders toward nondepressed control levels [151]. In another human study, MA in headache patients significantly reduced serum levels of IL-1 β , IL-6, and TNF- α to levels of nonheadache controls [152]. These acupuncture-induced changes in inflammation may be promising for treating the proinflammatory state seen in PTSD.

Genetics

A few human and animal studies have specifically evaluated gene expression changes following acupuncture treatment in cells from blood, brain, and liver. The genes in these studies have not been found to be differentially expressed in PTSD, because the studies were not about PTSD. However, all of the included genes in these studies have transcriptional control of proteins relevant to known PTSD pathology. Further research is needed to determine if these genes are differentially expressed in PTSD compared to appropriate control subjects. In one human study, 18 patients with allergic rhinitis received acupuncture 8 times over a 4-week period, which significantly reduced symptoms and mRNA levels for IL-1 receptor-alpha in peripheral blood cells at 2 h, 24 h, and 4 weeks after treatment [153]. In another study of 30 healthy volunteers, Liu and Yang found that the reinforcing method but not the reducing method of MA significantly increased the level of signal transducer and activator of transcription 5A in mononuclear cells [154]. Son and colleagues investigated the antipyretic action of MA in rats and found that acupuncture can suppress hypothalamic production of the proinflammatory cytokines IL-6 and IL-1 β at the level of gene expression: fever induced by lipopolysaccharide (LPS) injection was diminished by acupuncture, as were LPS-induced elevations in hypothalamic mRNA levels of these cytokines [155]. Another study found that EA upregulates IL-6 mRNA levels in rat cortex and striatum following cerebral ischemia-reperfusion, but sham acupuncture does not [156]. Rho and colleagues measured hypothalamic gene expression in healthy rats receiving EA applied to the common point ST36 and found elevated mRNA levels for genes related to pain, including the serotonin receptor 3A [157]. Several published studies that measured protein expression levels for transcription factors and neuropeptides in rat brain also provide indirect evidence of acupuncture-induced gene regulation. For example, Park and colleagues found that MA attenuates postnatal separation stress induced increases in neuropeptide Y (NPY) levels in the basolateral amygdala of rat pups, indicating that acupuncture can reduce anxiety-like behavior by modulating the NPY system in the amygdala [158]. Another study with rats found that EA during immobilization stress significantly attenuated stress-induced expression of the transcription factor c-fos in the paraventricular hypothalamic nucleus, supraoptic nucleus, suprachiasmatic nucleus, medial amygdaloid nucleus, lateral septum, and the LC [159].

Conclusions

Conceptual, clinical, and biological data support the potential efficacy of acupuncture for PTSD. CM, like MWM, identifies stressful

events and individual variables in a developmental framework as causal to PTSD. Similarly, both conceptualize PTSD as a complex, heterogeneous illness, although there is only preliminary conceptual data from the CM perspective. In both traditions, the field will benefit from identifying core clinical and biological features that are more specific to PTSD. In both traditions, but particularly regarding CM and acupuncture, trials are needed to better understand associated clinical and biological outcomes. To be able to support the use of acupuncture for PTSD in health care systems, definitive placebo-controlled and comparative effectiveness clinical trials are needed.

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Conflict of Interest

The authors have no conflict of interest.

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