Acupuncture in the Treatment of Post-Traumatic Stress Disorder: A Neurobiological Approach
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Post-traumatic Stress Disorder (PTSD) awareness has seen an upsurge in recent decades and correlations with brain injuries within military populations, community, or mass traumas. The national prevalence in the United States is an estimated 7-9% of the population being affected.[1] This percentage increases in populations with a higher risk of repeated exposure to traumatic events such as paramedics, firefighters, etc. ranging from 17-22%. If the individual has sustained a head injury, either due to an automobile accident, or some other cause sample rates ranged from 13-33% developing some degree of PTSD. Military personnel are estimated to range in rates from 10-30% with combat exposure further increasing the risk and being a primary determinant compared to deployment without combat exposure. Due to the increased numbers of blast injuries, head injuries and PTSD are becoming increasingly comorbid occurrences. It has been reported in a 2008 study that 43.9% of personnel who reported a TBI with loss of consciousness met criteria for PTSD.[2]

The after-effect of a stressful situation can cause a chronic complex of emotional and physical symptoms in which one re-experiences an overwhelming traumatic event. This causes intense fear, helplessness, horror, and avoidance of stimuli associated with the trauma. PTSD acts as a continuation and magnification of anxiety-related symptoms which fit into three primary symptom clusters – reexperiencing, avoidance symptoms, and hyperarousal. In order to meet diagnostic criteria these symptoms must be present for at least one month and impair the individual's ability to function in a social, occupational or other important life arena.

Diagnostic criteria for PTSD	
Activity	**Possible Symptoms**
Exposure to or witnessing of a threatening event	Intense fear Helplessness Horror Symptoms of reexperiencing
Recurrent or intrusive memories	Nightmares Sense of reliving the trauma Psychological or physiological distress when reminded of the trauma
Avoidance	Inability to recall parts of the trauma Withdrawal Emotional numbing
Increased autonomic arousal	Sleep disturbance Irritability Hypervigilance Difficulty concentrating Exaggerated startle response

Factors in the development of PTSD	
Pre-traumatic factors	-Ongoing life stress or demographics -Lack of social support -Young age at time of trauma

	-Pre-existing psychiatric disorder -Low socio-economic status, education level, intelligence, gender -Prior trauma exposure (reported abuse in childhood, report of other previous traumatization, report of other adverse childhood factors -Family history of psychiatric disorders
Peri-traumatic or trauma related factors	-Severe trauma -Type of trauma (interpesonal traumas such as torture, rape or assault convey a high risk of PTSD) -High perceived threat to life -Community (mass) trauma -Peritraumatic dissociation
Post-traumatic factors	-Ongoing life stress -Lack of positive social support -Negative social support (ex: negative reactions from others) -Bereavement -Major loss of resources -Other factors, including children at home and distressed spouse

Physical changes to cortical structures, including connectivity, activation intensity, and tissue volume loss have been demonstrated to occur as a result of experiencing trauma and will be explored below.. Many symptoms that present in cases of PTSD have similarities to, or are also found in traumatic or acquired brain injuries such as cognitive impairments (poor attention and memory), behavioral components (impulsivity, disinhibition) and emotional changes (emotional lability, depression). Secondary effects such as social isolation, difficulty in interpersonal relations, and impairments in functioning in home and work environments may also become problematic. This overlap in symptoms can make differential diagnosis between the two difficult. It is possible that the similarities in symptomology relate to similarities in brain regions and functions affected by both conditions as discussed below. In cases where both are present it has been proposed that a brain injury compromises the individual's ability to cope with the stress of PTSD through disinhibition of executive function while PTSD compromises the ability to navigate some of the cognitive difficulties that can follow a brain injury. As a result, this interplay can be difficult for an individual to manage. Silver[1] states the best explanation of the dynamic between the two disorders is “that the unique interface between the central nervous system and concurrent psychological distress leads to signs and symptoms that are characteristic of both post-concussion and PTSD. In addition, this relationship is dynamic, and the relative contributions of etiological factors contributing to the symptoms change over time.”

Comparison of symptoms between PTSD and brain injury		
PTSD	Found in both PTSD and Brain Injury	Brain Injury

Flashbacks Avoidance Hypervigilance Nightmares Reexperiencing	Fatigue Irritability Insomnia Depression Cognitive deficits	Headache Nausea/vomiting Photophobia or noise sensitivity Vision problems

Types of stressors that can induce PTSD:
- Threat to one's life or physical integrity
- Serious threat or harm to one's children, spouse, other close relatives, or friends
- Destruction of one's home or community
- Seeing another person who is mutilated, dying, or dead
- Being the victim of physical violence (including child abuse)

Common Biomedical Intervention[2]
Anti Depressants (SSRI's)
-Fluoxetine
-Sertaline
-Partoxetine
Mood Stabilizers – Lamotrigine
Atypical antipsychotics – Olanzapine
Beta-blockers - Propanalol
Psychotherapy
-Cognitive-behavioral (individual and group, trauma-focused or traditional)
-Exposure Therapy
-Stress management

Associated Neuropathology
Brain regions most often affected by PTSD include the medial prefrontal cortex, anterior cingulate cortex, temporal region, insular cortex, hippocampus and the amygdala. It has been proposed that PTSD is characterized by an exaggerated amgydaloid response coupled with impairments in regulation of the medial prefrontal cortex (hypoactivation in the dorsal and rostral anterior cingulate and ventromedial prefrontal cortex) which fails to inhibit the heightened fear reactions of the amygdala.[3] Directionality of these reward network effects, which are responsible for abnormal responses in PTSD, is unknown. This is to say, it has not been determined whether the amygdala is solely overactive, leading to *relatively* decreased frontal activity, or an underactive frontal region fails to suppress amygdala responses, or a combination of the two occur.[4] This interplay between regions likely leads to the problems seen with heightened responsivity to threat and altered emotional control[4].

It has been further hypothesized that impairment of executive function due to injury of the frontal lobe increases the perseverance of the re-experiencing effect. Altered activities in the visual areas have been related to processing of visual imagery in PTSD patients. Hippocampal and parahippocampal atrophy has also been correlated to PTSD as demonstrated by volumetric studies and magnetic resonance spectroscopy. This seems to be a phenomena that occurs primarily in the right hemisphere in Vietnam combat veterans with an 18% decrease. Interestingly, this hippocampal atrophy was demonstrated to be a left hemisphere occurrence in women who experienced childhood sexual abuse. This atrophy does not occur within the first six months post-injury but rather a while after the event and does not seem to occur in children.

A meta-analysis looking at adaptive differences between single trauma events and prolonged trauma revealed that in single-incident traumas the bilateral medial pre-frontal cortex, anterior cingulate cortex, striatum, insula and the left hippocampus and amygdala seemed to be most affected. Prolonged traumas on the other hand were found with primary involvement of the left striatum, insula, amygdala, and medial temporal gyrus, but not within the medial pre-frontal cortex (mPFC). It was speculated it may be that prolonged and repetitive trauma exposure may not be mediated by the mPFC-limbic network[5], but by the striatum and insula instead[6]. Increased functional connectivity between striatum and insular cortices have been demonstrated during repeated trauma. The study suggested a different neural mechanism may underlie PTSD by prolonged traumas. Some studies on grey matter changes in PTSD have provided evidence that illness duration was significantly associated with right hippocampal volume decreases[7,8].

A study of cortical thickness which accounted for size, density, and arrangement of neurons, glial cells and nerve fibers in recent-onset PTSD cases found cortical thinning occurred in the bilateral hippocampus, anterior cingulate gyrus, posterior cingulate gyrus, left inferior and right superior parietal lobes, left superior frontal lobe, and right superior rostral middle frontal gyrus. Cortical thickening in recent onset PTSD patients was only found within the left calcarine cortex.[9] Results from a study of soldiers with PTSD were compared to those from age- and experience-matched soldier controls. It was found that the PTSD diagnosis is accompanied by reduced cortical thickness, primarily in the frontal and temporal gyri, decreased relative volumes of the caudate, but relative enlargement in several lobules withing the cerebellum. It was speculated that "since CT reflects the number, density, and size of neurons, [10, 11] a reduction in CT may be interpreted as a loss of dendritic spines or a change in the cortical mantle due to a decrease in neuronal number."[4]

Electroencephalography (EEG) studies have revealed various notable variations in PTSD cases. PTSD patients with childhood trauma showed an overall enhanced alpha and beta band coherence over the central and temporal regions.[12] Another study showed increased alpha band functional connectivity between the precuneus and the right inferior parietal lobe in PTSD. The precuneus has been correlated with a number of functions including mental imagery of the self as in reflective self-awareness and rating one's own personality traits, episodic memory, and visuospatial imagery. In a study of both global and nodal level functional networks a number of significant findings were found between individuals with PTSD and control subjects. Globally there was a demonstrated decrease in strength, clustering coefficient and efficiency in the delta, theta and low beta signals. In these same bands there was a demonstrated increased path length. It is hypothesized this may imply disrupted clustering and inefficiently increased connectedness of brain networks in PTSD. There were no significant differences found between PTSD patients without and those with comorbidities. Nodal level clustering coefficient differences were then gauged at the delta, theta and low beta bands based on the globally demonstrated decrease. Significant differences from control patients were as follows:

Delta Band	Theta Band	Low Beta Band
Frontal (BA8) Temporal (BA21 and BA41)	Frontal (BA11 and BA 44) Occipital (BA8) Posterior Cingulate Cortex (BL23; PCC) Temporal (BA21, BA38, and BA41) Primary Somatosensory Cortex (BA1-3)	Frontal (BA44) Anterior Cingulate (BA24 and BA32) Parietal (BA7 and 40) Temporal (BA37) Occipital cortex (BA17 and BA18)

Diminished delta sleep responses in PTSD patients is intimately associated with hypothalamic corticotropin-releasing factor (CRF) and this may be indicated by the decreased clustering coefficient.[13, 14]

The Theta band differences were negatively correlated with symptom scores reflecting rumination and re-experiencing. Other studies have shown relationships between negative memory and rumination and between rumination and event scale symptoms.[15] fMRI studies have demonstrated negative memory to be related to the hippocampus, frontal cortex, posterior cingulate, and anterior cingulate. These regions have also been associated with rumination,[16] alongside associations with temporal lobe activity.[17] Theta oscillations arising from the amygdala-hippocampal pathway during fear memory conditions[18] and theta band connectivity have been associated with personal rumination, rather than nominal rumination.

The clustering coefficient differences in the low beta band positively correlated with symptoms scores reflecting anxiety and pain symptoms. Multiple studies have reported combat veterans with PTSD to have increased central region beta activity.[19,20] It has also been demonstrated to occur during sleep in individuals who had experienced maltreatment in childhood.[21] It has been argued that the anterior cingulate plays an important role in anxious symptoms[22] while others have reported reduced activity in the anterior cingulate and frontal cortex having an association with altered emotional modulation. Differences demonstrated among the somatosensory association cortex was found to correlate with Pain Anxiety Symptoms Scale (PASS) scores and seem to reflect anxiety and pain symptoms.

Neurochemical changes associated with PTSD involve multiple neurotransmitter pathways. The role of seritonergic pathways in this process have a significant body of evidence.[23, 24] The regions most sensitive to serotonin include the limbic system and frontal-subcortical circuits. SSRI's have often been used for PTSD symptoms as benefits have been demonstrated. These SSRIs also modulate the release of norepinephrine which directly impacts startle response, the prefrontal cortex inhibition of the amygdala, and release with recollection of the traumatic event; all of which create a feedback loop of consolidation of the memory.[25] Additionally, GABA has been demonstrated to be downregulated and the excitotoxic neurotransmitter, glutamate, increased[26.] Acetylcholine regulation may also be impacted and have a significant effect on cognitive symptoms due to it's supporting role in the reticular formation involved in arousal and attention, the entorhinal-hippocampal formation involved in declarative memory, and the frontal-subcortical circuits involved in executive functioning.

Endocrine changes associated with PTSD show that individuals tend to have low basal cortisol levels with high levels of corticotropin-releasing factor (CRF). This is interesting as a classic stress response involves elevated levels of CRF, ACTH, and cortisol. This was originally attributed to the idea of adrenal fatigue following the acute injury/trauma, but emergency room studies have shown low to normal levels of cortisol as well. It has been shown that those with PTSD have an increased number of glucocorticoid receptors and that these receptors demonstrated an increased sensitivity. Changes such as these allow for a greater inhibition of cortisol through negative feedback at the pituitary gland with less ACTH being released, and the subsequent attenuation of cortisol. Primary effects on the central nervous system of blast injuries were indicated by elevated levels of eicosanoids and stress hormones.

Cortisol, neuroanatomical substrates and structural, volumetric changes (PTSD 8)
Cortisol is a steroid hormone of the adrenal complex which acts as the primary stress hormone and participates in the regulation of metabolism of carbohydrates, fats, and proteins as well as inflammatory processes. During stress the hypothalamic-pituitary-adrenal axis becomes activated. If the acute stress is not removed and becomes chronic, prolonged cortisol secretion can lead to suppression of the

immune system and one may become prone to various diseases, increased infections, autoimmune reactions, or neoplasm risk. Altered cortisol concentrations may create endocrine imbalances with increased sensitivity of the liver. This produces insulin and increased blood glucose levels.[27]

Hypercortisolism and associated cognitive deficits are also associated with obsessive compulsive disorder, panic disorder, or melancholic depression with reduced ability for cortisol receptors to bind in the hippocampus, affecting memory and consciousness. Excessive cortisol production can lead to hippocampal atrophy. This has been found clinically in a number of different dissociative disorders[28]. Yehuda et al.[29] showed the correlation of chronic stress and post-traumatic stress disorder with lower basal cortisol levels by exhaustion of the hypothalamic-pituitary-adrenal axis. Other research has shown that there is increased secretion of cortisol in those with PTSD. Studies monitoring course and development of PTSD in abused children showed increased secretion of cortisol due to the experienced and re-experienced trauma. This suggests that the lowered levels of circulating basal cortisol may occur until a person develops a mechanism leading either to healing, in the sense that they will not develop PTSD, or to triggering the effects of increased cortisol concentrations in response to stress and subsequently development of some somatic or psychiatric disorder like PTSD. Starcevic et al.[30] documented decreased levels of cortisol, which induced decreased volumes of, especially, left amygdala, right putamen, total hippocampal volume, and prefrontal cortex.

Hippocampus

The hippocampus, a brain area involved in learning and memory, is situated in the medial temporal lobe just under the cortical surface. Under normal conditions, the hippocampus acts to blend together all elements of a memory from all the sensory areas. Short-term memories become stored within the hippocampus. When they are no longer required as conscious memories, the hippocampus processes these into other parts of the brain to create longer term memories. The hippocampus contains high levels of glucocorticoid receptors which make it more vulnerable to chronic stress than most other brain areas[31]. Stress related steroids like cortisol affect the hippocampus by reducing the excitability of some hippocampal neurons, inhibiting the neurogenesis in the dentate gyrus and causing atrophy of dendrites in pyramidal cells of the specific CA3 region. This leads to the determination that humans who have experienced chronic traumatic stress develop atrophy of the hippocampus more often than of other parts of the brain. Studies have the possibility of serotonin acting through excitatory amino acids to mediate hippocampal atrophy. Magnetic resonance imaging (MRI) studies have shown a reduction in volume of the hippocampus in both combat veterans and victims of childhood abuse[32, 33, 34]. In combat veterans, the hippocampal volume reduction was correlated with deficits in verbal memory on neuropsychological testing.[35, 36, 37]. All of the above mentioned cortical changes have been found to be present in post-traumatic stress disorder[38]. Hippocampal damage interferes with the proper processing of information coming from the amygdala making an individual vulnerable to new disturbing stimuli.[39-41]

The volume reduction of the hippocampal formation may be explained by a negative impact of cortisol at the level of the hippocampal cells[42, 43]. Intense stress is associated with the release of endogenous stress hormones and transmitters of cortisol, epinephrine, and norepinephrine, vasopressin, oxytocin, and endogenous opiates. Their role is reflected in the launch of altered metabolism and release of energy necessary to respond to stress. In a healthy organism, these changes occur only for a short duration, and the baseline cortisol level of functioning is established as soon as the danger has passed. In cases of prolonged stress, if it is very intense, there occurs a dysfunction of the system response to stress and to its desensitization[44].

Investigations of neurohormonal functions in post-traumatic stress disorder show reactions that are the opposite of the normally expected responses to stress. In acute stress glucocorticoids and catecholamines modulate the reciprocal effects that regulate cortisol stress hormones via negative feedback through the hippocampus, hypothalamus, and pituitary gland. Researchers have suggested that cortisol is a potent hormone that can even interfere with other processes in the body after the exposure to acute stress[42, 43, 45].

Alternately, released catecholamines and corticosteroids stimulate active behaviors necessary to overcome stress. In the case of low levels of corticosteroids, the increased irritability is caused by inadequate and uncontrolled reactions of fight or flight. Chronic stress induces decreased basal cortisol levels. On the other hand, acute stress can be seen as a leading factor of decreased activation of pulsatile stress hormone release, and increased number of glucocorticoid receptors in the hippocampus structure[45]. Kuljić and colleagues showed in their rat studies that chronic stress caused a reduction in corticosterone concentration indicating exhaustion of the hypothalamic-pituitary-adrenal axis[46].

A study conducted by Resnick et al.[47] showed that reduced cortisol levels made people more susceptible to post-traumatic stress disorder, for example, those with a personal history of sexual abuse[47].

Amygdala

The amygdala is considered a primary center of normal emotional expression to external stimuli and the realistic perception and response to stress and fear. Exposure to a traumatic event results in autonomic activation, after which the amygdala evaluates that information, determines its emotional significance, and triggers a further structure such as hypothalamus, hippocampus, and basal prosencephalon. This will determine the behavioral, autonomic and neurohormonal function and its manifestation. LeDoux[41] discovered a crucial role of the amygdala in the emotional brain, which he called “neural alarm”, in which the limbic response can take control over behavior even when the prefrontal cortex is still at the stage of selecting an equal reaction to external stimulation, essentially “overriding” the prefrontal cortex. A study conducted on forty-nine male patients, Starcevic et al.[48], found that both left and right amygdala volumes were statistically significantly different between individuals with PTSD and individuals without PTSD. While effects were bilateral, the left amygdala showed a greater impact in volume changes. Rogers et al.[49] show that the left amygdala volume has a significant negative correlation with the severity of PTSD symptomatology as well as with the reduced grey matter density in the left anterior cingulate cortex. A smaller amygdala volume was associated with the presence of cancer-related intrusive recollections in a sample of 76 breast cancer survivors[50]. Normal amygdala volumes do not necessarily preclude functional abnormalities in the amygdala in those with PTSD. For example, in a functional neuroimaging meta-analysis of participants with PTSD with amygdala abnormalities, particularly in the left amygdala, two distinct clusters of abnormal function were identified: a ventral anterior hyperactivation cluster and a dorsal posterior hypoactivation cluster[51,52].

Prefrontal cortex

The prefrontal cortex, a cortical structure which rests anterior to and covers the front part of the frontal lobe, is responsible for executive functioning tasks such as decision-making, multi-tasking, and judgment tasks. It has been indicated as an integral link between an individual's personality and basic psychological functions of the frontal cortex[54]. Brain imaging studies have demonstrated reduced volume and interconnections of the frontal lobes with other cerebral regions in individuals with different mental disorders such as post-traumatic stress disorder[55, 56]. Researchers, who have studied the prefrontal cortex as a part of the brain that suppresses memories, showed that it was unable to preoperly

operate at lower levels in people with stress related disorders when compared to healthy subjects. When individuals with stress-related disorders were asked to suppress their memory of certain words, their brains showed higher than normal hippocampal activation[57].

Volume reduction of this brain region may occur as a result of molecular alterations here. Studies [57,58] showed increased blood flow in the upper prefrontal region of the brain in a study conducted on both men and women who suffered from posttraumatic stress disorder.

Striatum: Caudate nucleus, putamen, and globus pallidus
Subcortical structures such as the caudate nucleus and putamen have been described as being involved not only in motor function, but in cognitive processes as well with volume decreases being associated with major depression and Alzheimer's disease. Negative effects of cortisol together with dehydroepiandrosterone result in volume decrease of these subcortical structures[59].

Globus pallidus, as a major subcortical grey structure, participates in the regulation of sleep via the nigrostriatal dopamine and through its connections with subthalamic nucleus[60]. Studies carried out on a rat experimental model have shown that damage to the globus pallidus leads to disruption of sleep. Sleep disorders, which can occur as severe symptoms of PTSD, lead to hypoxic and metabolic changes in the brain. This further results in an altering of dopamine levels and the degree of blood flow through the brain, which then, in turn, leads to brain atrophy[61].

Insula
The insula is responsible for passing interoceptive information into the brain to create a concept of self-awareness in the present moment. It utilizes information on internal states to integrate the sensory and somatic experiences of emotions. Physical sensation accounts for approximately 60% of an emotional experience via the viscerosensory cortex.[62] This plays an important role in the experience of stress, anxiety, or nervousness. If cortical connections between the insula and amygdala become overactive it may elicit anxious feelings in an individual.[63, 64] Lowered insular activity will result in the individual finding it difficult to put their experience into words due to a disconnect between the sensory signals coming in and the ability to effectively process it into a mental construct of experience. They may feel disconnected from or “not in” their body. In PTSD, individuals may feel “numb”, with no access to their feelings. This may result in gustatory disconnect and associated anorexia. Other symptoms which elicit greater physical sensory stimuli such as self-harm may also occur. Excessive insular activity will often result in individual's having a difficult time removing themselves or moving on from the sensation. They will dwell on it excessively.[64, 65]

Examination of PTSD studies of the insula confirms increased activation of the right middle insula in a sample of women with intimate partner violence-related PTSD.[66] Other studies have also shown increased activation of the insula [67, 68]. Findings of higher insula activation also extend to emotional, trauma-unrelated stimuli [69,70]. Analyses have confirmed later childhood early life stress (ELS) events to be associated with volumetric reductions in the ACC and insula volumes, while ELS experienced between the ages of 1 month and 7 years was not associated with lower brain volumes in these regions. This may reflect the influence of more fully developed emotional processing of ELS on the developing brain implicating both the anterior cingulate cortex and insula in neuropsychiatric disorders and emotional regulation[71]. Given the dense cortical connections between the insula and amygdala in regulating the autonomic nervous system, the role it may play in fear conditioning and PTSD is very pertinent. Though the amygdala is a key component of the fear response, the insula has been found to be involved in more generalized anxiety responses, including interoceptive and anticipatory anxiety [72]. The combination of the amygdala and insula then appears to have a unique and complementary role in

limbic and emotional processing [73]

Anterior Cingulate Cortex
The anterior cingulate may serve a critical gating function in modulating conditioned fear responses. As such, this region would be a key component of a neural circuit involved in the pathophysiology of PTSD. Volume decreases in the right anterior cingulate gyrus have been demonstrated in patients with PTSD when compared to non-PTSD subjects[74]. The anterior cingulate may serve a critical gating function in modulating conditioned fear responses. As such, this region would be a key component of a neural circuit involved in the pathophysiology of PTSD. An amygdala-locus coeruleus-anterior cingulate circuit may be consistent with evidence for chronic noradrenergic activation documented in PTSD patients. According to this model, efferent noradrenergic projections from the locus coeruleus may dampen anterior cingulate function. This in turn would allow myriad external or internally driven stimuli to produce the exaggerated emotional and behavioral responses characteristic of PTSD.[75]

Superior Temporal Gyrus
Unadjusted superior temporal gyrus grey matter volumes were larger in maltreated subjects with PTSD than in control subjects. White matter volumes in the superior temporal gyrus, however, were smaller in maltreated subjects with PTSD than in control subjects. After adjusting for differences in cerebral volume, right, left, and total superior temporal gyrus volumes were relatively larger in PTSD subjects compared with control subjects. After covarying for differences in cerebral grey matter volumes, regression analysis showed that PTSD subjects had significantly greater superior temporal gyrus grey matter volumes in most, and particularly in right-sided superior temporal gyrus measurements. Furthermore, findings of analysis superior temporal gyrus volumes suggest that there is a more pronounced right > left asymmetry in total and posterior superior temporal gyrus volumes but a loss of the left > right asymmetry seen in total, anterior, and posterior superior temporal gyrus grey matter volumes in PTSD subjects compared with control subjects. [76]

Cerebellum
It has been hypothesized that individuals with PTSD would show functional and anatomical alterations within core nodes of networks spanning the entire brain, including default mode, central executive and salience networks.[77] Using tensor based morphometry (TBM), significantly smaller volume in the right cerebellar crus in the PTSD compared to healthy group was revealed. Follow-up seed connectivity indicated weaker connectivity within major nodes of the central executive network (left and right dorsolateral prefrontal cortex) in the PTSD sample. Individuals with PTSD also exhibited weaker connectivity between nodes of the default mode network (medial prefrontal cortex and cerebellum) and the supramarginal gyrus. Convergent findings from neuroimaging and lesion studies have led to a reconceptualization of the cerebellum as playing an important role in cognition and emotion.[78-80]

A correlation between functional connectivity in the cerebellum and both overall symptom severity and severity in the four symptom domains specified in the DSM-5 (intrusion symptoms, avoidance, NACM and hyperarousal), suggesting a non-specific role for the cerebellum in PTSD symptomatology.[77] Lesions to the cerebellum can result in anxiety, aggression, irritability and distractibility,[81] symptoms that are relevant to PTSD. Structural and functional cerebellar abnormalities in PTSD have been reported previously wherein cerebellar volume has been shown to be lower in adolescents [82] and adults with PTSD,[83, 84] with cerebellum volume negatively correlating with PTSD symptoms. Increasing cortical excitability in the dorsolateral prefrontal cortex through active repetitive transcranial magnetic stimulation was associated with a significant reduction in PTSD symptoms.[85] Reduced medial prefrontal cortex function in PTSD has been linked to disturbances within the default mode network,[86, 87,] which is associated with internally focused thought, autobiographical memory and mind-wandering,

and whose activity is typically increased in the absence of a cognitively-demanding task.[88]

A weakened default mode network could be associated with disrupted self-referential processing, which can lead to dissociative symptoms and impairments in autobiographical memory, both of which have been implicated in PTSD.[89] The reduced connectivity in medial prefrontal cortex and in the cerebellum, a peripheral component of the default mode network[90-92] adds to the growing literature implicating dysfunction of the default mode network in PTSD.[85, 86, 93] Furthermore, observed reduced anatomical covariance with the middle temporal gyrus, also part of the default mode network has been observed[94]

Neurobiological Foundations of Acupuncture Approaches In PTSD

A growing body of evidence is being presented in acupuncture's potential role as an effective treatment approach to help individual's affected by PTSD. A systematic review synthesized evidence from seven studies which met criteria with 709 total participants included that compared acupuncture with "treatment as usual", sham acupuncture, a passive waitlist control, cognitive behavioral therapy, and paroxetine use. The review showed statistically significant effects in favor of acupuncture (as adjunctive or monotherapy) versus any comparator for PTSD symptoms at post-intervention[95]. A systematic review of randomized control trials showed a high-quality trial reporting acupuncture as superior to wait list control, with therapeutic effects of acupuncture and cognitive-behavioral therapy (CBT) being similar based on the effect sizes. Another randomized control trial reported a favorable effect of acupoint stimulation plus cognitive behavioral therapy (CBT) against CBT alone. A meta-analysis of acupuncture plus moxibustion versus selective-serotonin reuptake inhibitors favored acupuncture plus moxibustion in three outcomes. The systematic review concluded "that the evidence of effectiveness of acupuncture for PTSD is encouraging"[96]. The Journal of Mental and Nervous Diseases published a study evaluating the possible efficacy and acceptability of acupuncture for PTSD in which people diagnosed with PTSD were randomized to either an empirically developed acupuncture treatment, a group cognitive-behavioral therapy, or a wait-list control. Based on self-reported PTSD symptom measures at baseline, end treatment, and 3-month follow-up it was found that compared to the wait list group, acupuncture provided large treatment effects for PTSD similar in magnitude to the cognitive behavioral group. Symptom reductions at end treatment were maintained at 3-month follow-up for both interventions.[97]

In population specific studies, one study of fifty-five service members meeting research diagnostic criteria for PTSD were randomized to usual PTSD care plus eight 60-minute sessions of acupuncture conducted twice weekly or usual care alone. Outcomes were assessed at baseline and 4, 8, and 12 weeks post-randomization and found mean improvement in PTSD severity was significantly greater among those receiving acupuncture than in those receiving usual care. Acupuncture was also associated with significantly greater improvements in depression, pain, and physical and mental health functioning[98]. Another study of 138 patients with earthquake-induced PTSD who enrolled were randomly assigned to an electroacupuncture group and an oral paroxetine group. The electro-acupuncture group was treated by scalp electroacupuncture with safety and efficacy of electroacupuncture evaluated using Clinician-Administered PTSD Scale (CAPS), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Treatment Emergent Symptom Scale (TESS). Efficacy in the electroacupuncture group was found significantly better than that in the paroxetine group.[99]

Postulated Acupuncture Mechanisms in PTSD

A number of bioregulatory mechanisms of acupuncture in PTSD will be postulated and explored. These include:

-Initiation of endogenous opioid secretion to reduce pain
-Regulation of amino acids and neurotransmitters to down regulate the sympathetic response
-Upregulation of nerve growth factor and increased neuroplasticity
-Redirection of blood flow from the limbic system to the prefrontal cortex
-Inhibition the amygdala and insula to alleviate hyper-vigilance and heightened fear response
-Bioregulatory effect of sympathetic and parasympathetic responses

Acupuncture Effect and Neurohumoral Modulation

Some neurotransmitters, including serotonin, norepinephrine, opioid peptides, catecholamines, and amino acids in the brain appear to participate in the modulation mechanism of acupuncture for certain components of the autonomic nervous system [100,101,102]

Endogenous opioids

Acupuncture has been shown to mediate endogenous opioid pathways[103,104]. Activation of enkephalinergic neurons in several brain areas that regulate sympathetic outflow have been demonstrated, including the arcuate nucleus, rostral ventrolateral medulla, raphé nuclei, among others[105,106]. Li et al.[107] found that electroacupuncture at P5-P6 transiently stimulates the production of enkephalin in a region of the brain which regulates sympathetic outflow. It is suggested that a single brief acupuncture treatment can increase the expression of this modulatory neuropeptide. The β-endorphin is a key mediator of changes in autonomic functions[108]. Acupuncture may affect the hypothalamic-pituitary-adrenal (HPA) axis by decreasing cortisol concentrations and the hypothalamic-pituitary-gonadal (HPG) axis by modulating central β-endorphin production and secretion[109]. The hypothalamus is one of the largest manufacturers of beta-endorphins, the body's endogenous poly-opioids which reduce pain. These opiod substances immediately travel to the periaqueductal grey to depress all pain signaling from the periphery. Serotonin is also released in the brainstem and stimulates further serotonin releases, along with norepinephrine within the dorsal horn. Both of these strongly inhibit pain signaling in both directions.[110]

Amino Acids

Amino acid sensors could regulate the activity of vagal afferent fibers as they are directly involved in signaling the vagus pathway in the arcuate nucleus[111]. Studies conducted so far on amino acids suggest that glutamate and GABA are involved in the mechanism of acupuncture for autonomic alteration closely related to ventrolateral periaqueductal grey. Recent studies have shown that vesicular glutamate transporter 3 (VGLUT3) in the arcuate nucleus neurons[112,113] and ventrolateral periaqueductal grey[105,114] were activated by electroacupuncture at the P5-P6 acupoints. Glutamate only partially, but significantly, contributes to the activation of arcuate nucleus-ventrolateral periaquaductal gray reciprocal pathways during electroacupuncture stimulation of somatic afferents[115]. Electroacupuncture modulates the sympathoexcitatory reflex responses by decreasing the release of GABA in the ventrolateral periaqueductal grey[116], which disinhibits ventrolateral periaqueductal grey cells, in turn, modulating the activity of rostal ventrolateral medulla neurons to attenuate the sympathoexcitatory reflex responses.

Nerve Growth Factor (NGF)

The nerve growth factor is a neurotrophin, which regulates the function and survival of peripheral sensory, sympathetic, and forebrain cholinergic neurons. It is speculated to modulate sensory and autonomic activity as a mediator of acupuncture effects in the central nervous system[117] by a long-lasting depression of the sympathetic branch, which is associated with a peripheral downregulation of

nerve growth factor in organs. Mannerås et al.[118] found that electroacupuncture could effectively improve poly-cystic ovarian syndrome (PCOS)-related metabolic disorders, alter sympathetic markers[119], and normalize the DHT-induced increase of mRNANGF. The data on electroacupuncture/nerve growth factor interaction in PCOS models further suggested that the decrease of nerve growth factor expression in peripheral organs could benefit by electroacupuncture to modulate the activity of the autonomic nervous system[120]. Although nerve growth factor in organs has been proved to be associated with the acupuncture effect on the autonomic nervous system, there is a lack of sufficient evidence to demonstrate the relationship between acupuncture effect and central nerve growth factor.

Acupuncture in autonomic regulation

Several studies have demonstrated that the autonomic dimension of acupuncture stimulation was mediated by a mesencephalic and brainstem network[121,122], made up primarily of the hypothalamus, medulla oblongata, ventrolateral periaqueductal grey, and the dorsomedial prefrontal cortex. All of these areas are involved in the autonomic regulation[123,124].

Hypothalamus

The hypothalamus has been shown to be involved in the pathway of electroacupuncture attenuating sympathetic activity with impulses generated in sensory fibers in the skin connecting with interneurons to modulate activities of the motoneurons hypothalamus to change autonomic functions[125]. Electroacupuncture at ST-36 has shown to modulate neuronal nitric oxide synthase activity in the hypothalamus in rat models. This may act through connections with the sympathetic and parasympathetic nervous system by decreasing neuropeptide Y production via the paraventricular nucleus, a cell group that plays an important role in the regulation of sympathetic vasomotor tone and autonomic stress responses[126,127]. Corticotropin-releasing hormone[128] expressions in the periventricular nucleus may also suppress the sympathetic outflow in response to chronic stressors[129].

Medulla Oblongata

Specific regions of the medulla oblongata mediate central control of autonomic functioning. Electroacupuncture could inhibit cardiovascular autonomic responses through modulating rostal ventrolateral medulla neurons[130,131] which play an important role in the sympathetic efferent limb of cardiovascular reflex activity and arterial blood pressure. Moreover, opioids and GABA participate in the long-term electroacupuncture-related inhibition of sympathoexcitatory cardiovascular responses in the rostal ventrolateral medulla[132]. Activation of the nucleus raphe pallidus attenuates sympathoexcitatory cardiovascular reflexes through a mechanism involving serotonergic neurons and 5-HT1A receptors in the rostal ventrolateral medulla during electroacupuncture.

The nucleus ambiguus, located in the ventrolateral division of the hindbrain, is considered to be an important site of origin of preganglionic parasympathetic vagal motor neurons that ultimately regulate autonomic function through the releasing of acetylcholine[132]. Some nucleus ambiguus neurons activated by electroacupuncture are preganglionic vagal neurons[133]. It has been suggested that stimulation on a particular acupoint is crucial to achieve modulate effect on autonomic function by activating nucleus ambiguus neurons.

Midbrain

The *v*entrolateral periaqueductal grey is an essential midbrain nuclei that processes information from somatic afferents during electroacupuncture[134]. Excitation of *v*entrolateral periaqueductal grey neurons enhances the arcuate response to splanchnic stimulation, while blockade of ventrolateral periaqueductal

grey neurons limits excitation of arcuate neurons by electroacupuncture. These observations indicate that electroacupuncture-induced excitation of arcuate neurons requires input from the ventrolateral periaqueductal grey, and the reciprocal reinforcement between the midbrain and the ventral hypothalamus serves to prolong the influence of electroacupuncture on the baseline blood pressure[135].

Dorsomedial Prefrontal Cortex (DMPFC)

The prefrontal cortex is vital for mediating behavioral and somatic responses to stress in the autonomic centers via projections[136]. A near-infrared spectroscopy study found that the right prefrontal cortex activity predominantly modulated sympathetic effects during a mental stress task[137]. It is speculated that acupuncture may decrease sympathetic activity and increase parasympathetic activity through its effects on dorsomedial prefrontal cortex activity[138].

Auricular Acupuncture In Autonomic Regulation

A number of various acupuncture protocols exist which utilize auricular acupuncture in treating trauma symptoms. Studies have shown that auricular acupuncture is able to regulate the autonomic nervous system[139, 140], elicit a vaso-vagal response[141], and activate the parasympathetic nervous system[142]. Below are some of the common auricolutherapy protocols with traditional point indications:

NADA: Shenmen, Sympathetic, Liver, Kidney, Lung
Battlefield Acupuncture: Shenmen, Point Zero, Omega 2, Thalamus, Cingulate Gyrus
Auricular Trauma Protocol: Shenmen, Point Zero, Hypothalamus, Hippocampus, Amygdada, Master Cerebral

Auricular Point Indications:
- Sympathetic- balances autonomic nervous system
- Shen Men – psychospiritual vitality, balance to Heart channel, hypersensitivity to needles
- Kidney- warms freeze response, find safety in self, restore vitality/reserves
- Liver- soften anger/hyper-vigilance, freeze fight response
- Hippocampus - ease mind's grip on traumatic memory, bring relief to hyperarousal/intrusive images
- Hypothalamus – stimulates parasympathetic nervous system, triggers HPA axis, important for attention/vigilance/arousal
- Amygdala - modulates expression of anger/fear/aggression/irritability
- Hippocampus - memory encoding/emotional experiences. Imp for memory/concentration
- Master Cerebral - psychoemotional/psychosomatic disorders, emotions around chronic pain, pain. Zones for Limbic system (memory, emotions, compulsive behavior) and pre-frontal cortex (concentration, decision making, initiating action).
- Point Zero – moves mind/body/emotions toward homeostasis

Regional Influence of acupuncture on cortical regions
A number of points have been demonstrated by fMRI studies to have a correlation to brain activity in the limbic system[143]
Activating:
Hippocampus: GB-34, GB-39, LR-3, LI4, CV-6, CV-12, ST-25
Hypothalamus: ST-36
Thalamus: ST-36, GB-34, GB-39
Cerebellum General: LR-3, GB-40, GB-34, GB-39, LI-4
SMA: ST-36 left side

Middle Frontal Gyrus: KI-3
Inferior Frontal Gyrus: KI-3

Deactivating:
Amygdala: ST-36
Hippocampus: ST-36
Thalamus: LR-3, GB-40
Medial Frontal Gyrus: ST-36 left side, LI-4
Dorsolateral Pre-frontal Gyrus: LI-4
Inferior frontal Gyrus – LR-3 left side
Middle Frontal Gyrus: LR-3 left side, [BL-60, 65, 66, 67 right side]

Tiaoshen Yizhi (*Harmonize the shen and benefit the intellect)*
Acupoints in this protocol, including *Sishencong* (EX-HN1), *Yintang* (EX-HN3), PC-6, KI-3, ST-40, LR-3 acupuncture in mild cognitive impairment patients showed central affected regions to be the insula, dorsolateral prefrontal cortex, and hippocampus. The insula received causal inflows from most nodes in the brain network, including the thalamus, hippocampus, anterior cingulate cortex, and primary somatosensory cortex. The hippocampus received causal inflows from the dorsolateral prefrontal cortex, anterior cingulate cortex, and medial prefrontal cortex. The dorsolateral prefrontal cortex received causal inflows from the orbitofrontal cortex, anterior cingulate cortex, and primary motor cortex.[144]

Acupoint ST-36
The limbic and paralimbic structures of cortical and subcortical regions in the elencephalon, diencephalon, brainstem and cerebellum demonstrated a concerted attenuation of signal intensity when the subjects experienced *deqi* after ST-36 was needled. The study provides preliminary evidence for an integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST-36 that correlates with the psychophysical response.[145]

Acupuncture stimulation induced fMRI-BOLD signal changes over extensive brain areas such as the hippocampus, hypothalamus, anterior cingulate cortex, posterior cingulate cortex, anterior insula, thalamus, and somatosensory region II. These results are consistent with previous fMRI studies, especially well-defined deactivation in the left amygdala[145]. Based on the activation study, three brain networks were defined in the ensuing connectivity analyses using the activated left amygdala as a reference. Findings showed an amygdala-associated brain network, consisting of extensive areas in the frontal gyrus, temporal gyrus, anterior cingulate cortex, posterior cingulate cortex, thalamus and basal ganglia. Aside from showing the overlapped regions with the above network, the post-acupuncture condition engaged other brain regions including the medial prefrontal cortex, postcentral gyrus, insula, and periaqueductal gray[146.]

Acupoint LI-4
Acupuncture needle manipulation performed at LI-4 on either hand produced prominent decreases in the nucleus accumbens, amygdala, hippocampus, parahippocampus, hypothalamus, ventral tegmental area, anterior cingulate gyrus (BA 24), caudate, putamen, temporal pole, and insula. Signal increases were observed primarily in the somatosensory cortex.[147]

Acupoint CV-6, CV-12

One study evaluating the effects of electroacupuncture on brain connectivity in cases of Crohns disease demonstrated that abdominal acupuncture at CV-6, ST-25, and CV-12 significantly increased resting state functional connectivity values between the bilateral hippocampus, anterior middle cingulate, anterior middle cingulate cortex, and insula[148].

Regional Acupuncture Effects

Limbic System

The combination effect of acupuncture and the antidepressant fluoxetine, as well as its underlying mechanism using resting state functional connectivity (rsFC) in patients with major depressive disorders was studied. Forty-six female depressed patients were randomized into a verum acupuncture plus fluoxetine or a sham acupuncture plus fluoxetine group for eight weeks. Verum acupuncture treatment patients using the points CV-4, CV-6. CV-10, CV-12, KI-17, ST-24, and Qipang showed 1) greater clinical improvement as indicated by Montgomery–Åsberg Depression Rating Scale (MADRS) and Self-Rating Depression Scale (SDS) scores; 2) increased rsFC between the left amygdala and subgenual anterior cingulate cortex/preguenual anterior cingulate cortex; 3) increased rsFC between the right amygdala and left parahippocampus (Para)/putamen. The strength of the amygdala-sgACC/pgACC rsFC was positively associated with corresponding clinical improvement. The additive effect of acupuncture to antidepressant treatment suggested this effect may be achieved through the limbic system, especially the amygdala and the anterior cingulate cortex[149].

Manual acupuncture at LI-4, ST-36, and LR-3 deactivates a limbic-paralimbic-neocortical brain network, while simultaneously activating somatosensory regions of the brain. Clusters of deactivation were found in the medial prefrontal, medial parietal and medial temporal lobes showing significant convergence of two or all three of the acupoints. The largest regions showing common responses to all three acupoints were the right subgenual BA25, right subgenual cingulate, right isthmus of the cingulum bundle, and right BA31. Differences were also noted in major sections of the medial prefrontal and medial temporal lobes, with LI-4 predominating in the pregenual cingulate and hippocampal formation, ST-36 predominating in the subgenual cingulate, and LR-3 predominating in the posterior hippocampus and posterior cingulate. Findings demonstrating preferential response of certain limbic-paralimbic structures suggests acupoints may also exhibit relative specificity. [150]

Hippocampus

In a meta-analysis of fMRI studies GB-34 and GB-39 had a demonstrated activating effect on the hippocampus.[151] In this same analysis ST-36 showed to have a downregulating effect on hippocampal structures. In a study analyzing hippocampal connectivity in patients with Alzheimer disease where frontal and temporal hippocampal activity was found to be decreased, acupuncture at LR-3 and LI-4 was shown to increase connectivity in most of these regions compared to resting state analysis.[152] Another study looked at LR-3, LI-4, and ST-36 in deactivating a limbic-paralimbic-neocortical brain network which found that acupuncture at LI-4 predominantly affected the pregenual cingulate and hippocampal formation while LR-3 predominantly affected the posterior hippocampus and posterior cingulate. ST-36 elicited responses primarily in the subgenal cingulate.[153]. One study evaluating the effects of electroacupuncture on brain connectivity in cases of Crohns disease demonstrated that abdominal acupuncture at CV-6, ST-25, and CV-12 significantly increased resting state functional connectivity values between the bilateral hippocampus, anterior middle cingulate, anterior middle cingulate cortex, and insula.[148]

Anterior Cingulate Cortex

In a study of Bell's palsy Acupuncture-induced functional connectivity changes of the contralateral anterior cingulate cortex (ACC) were observed for both early and later intervention groups. In the early

intervention group no remarkable changes of functional connectivity were found in the left ACC. Significant decreased connectivity of the right ACC after acupuncture were observed in right superior frontal gyrus, right middle frontal gyrus, and right middle frontal gyrus however. In the latter intervention group there were no significant changes of functional connectivity in the left ACC. Significant increased functional connectivity of the right ACC were observed in right superior temporal gyrus, right insula, right superior temporal gyrus, and right putamen in this group[154].

Amygdala

Significant fMRI signal changes have been demonstrated during acupuncture stimulation at ST-36 in the left amygdala, which was subsequently selected as a functional reference for connectivity analyses demonstrating a brain network associated with the amygdala during a resting condition. This network encompasses the brain structures that are implicated in both pain sensation and pain modulation. When compared with a sham acupuncture, verum acupuncture induced a higher level of correlations among the amygdala-associated network.[155,156]

Discussion

Based on presented studies, an evidence-based neurobiological basis for the treatment of PTSD with acupuncture can work to be developed. Protocols can be established based on evidence-based fMRI studies of cortical region activations and deactivations with acupuncture points correlating with findings and understandings of changes which tend to occur in the brain in cases of PTSD. This treatment approach would thus focus on the cerebellum, limbic structures including the amygdala and hippocampus, the anterior cingulate cortex, insula, and medial prefrontal cortex. Based on this criteria points that may be considered are LI-4, LR-3, ST-36, ST-40, PC-6, KI-3, GB-34, GB-39, CV-6. CV-12, Yintang, are Si Shen Cong. Given consideration of laterally brain regions affected and point effects, the following treatment protocol may be appropriate:

Left: LR-3, ST-40, GB-34, LI-4
Right: KI-3, ST-36, GB-39, PC-6
Bilateral: CV-6, CV-12,Yintang, Si Shen Cong
Total Points Used: 15

Auricular protocols as presented in this paper may also be considered in their bio-regulatory effect of the autonomic nervous system while being easily accessible and applicable high volume or group acupuncture situations. Recent studies using rodent models have suggested that acupuncture stimulates neurogenesis. In particular, stimulating the following acupoints by acupuncture or electroacupuncture appears to induce neuronal proliferation: ST-36, GV-20, PC-6, HT-7, CV-17, CV-12, CV-6, SP-10, GV-16, GV-8, LI-11, TW-5, and GB-30.[136] The mechanism for this is suggested to be the upregulation of brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, basic fibroblast growth factor and neuropeptide Y, and activation of the function of primo vascular system.[157] These points may also warrant consideration on this therapeutic effect alone.

Several limitations exist within this assessment which may hopefully be more thoroughly addressed with future research developments. Firstly, fMRI studies of cortical changes in response to specific acupuncture point stimulation, while growing in available data, remains limited. There has not been a wide assessment of the many acupuncture points used within the acupuncture system. Due to this, it is very possible there are a number of other acupuncture points that would elicit similar, or even more specific, cortical responses that have not been studied with an fMRI to determine these effects. This is a relatively new approach to acupuncture research and funding remains limited for these types of studies. Until a broader and more thorough analysis of cortical acupuncture point response has been done,

development of neurobiologically-based treatment protocols will remain limited to the available data. Secondly, while studies of the cortical changes and responses in PTSD have been more thoroughly assessed, this still remains a budding field of study and will no doubt have new information become available with continued research.

The purpose of this paper is designed to look at existing information and demonstrate that a neurobiological mechanism of acupuncture can be established in a PTSD model and that it is possible to apply these findings clinically. This allows the practitioner to be able to treat their patient with evidence-based treatment approaches based on objective, presentable data. This is not meant to supersede traditional acupuncture treatment approaches, diagnostics, or pattern differentiation, but to compliment them with an additional evidence-base. As this data becomes more available other protocols and evidence pools may be established for other medical conditions involving cortical structures including alzheimer's, dementia, multiple sclerosis, traumatic brain injury, etc.

REFERENCES

1. Silver, Jonathan, Yudofsky, Stuart, McAllister, Thomas. *Textbook of Traumatic Brain Injury*. Washington, DC: American Psychiatric Pub. 2011. Print.

2. Lash, Marilyn. *The Essential Brain Injury Guide*. 5th ed. Vienna, VA: Academy of Certified Brain Injury Specialists, Brain Injury Association of America. 2016. Print.

3. David J. Nutt, MD, PhD, and Andrea L. Malizia, MD, PhD Structural and Functional Brain Changes in Posttraumatic Stress Disorder. Web: *https://www.psychiatrist.com/jcp/article/Pages/2004/v65s01/v65s0103.aspx*

4. Sussman *et al.* Neuroanatomical features in soldiers with post-traumatic stress disorder. *BMC Neuroscience.* 2016; 17:13; DOI 10.1186/s12868-016-0247-x

5. Kim, J. J. & Yoon, K. S. Stress: metaplastic effects in the hippocampus. *Trends in neurosciences.* 1998; 21, 505–509.

6. Cisler, J. M. *et al.* Functional reorganization of neural networks during repeated exposure to the traumatic memory in posttraumatic stress disorder: an exploratory fMRI study. *Journal of psychiatric research.* 2014; 48, 47–55 (2014).

7. Chao, L. L., Yaffe, K., Samuelson, K. & Neylan, T. C. Hippocampal volume is inversely related to PTSD duration. *Psychiatry research* 2014; 222, 119–123.

8. Linghui Meng1,2, Jing Jiang1, Changfeng Jin3, Jia Liu1, Youjin Zhao1, Weina Wang1, Kaiming Li1 & Qiyong Gong1 Trauma-specific Grey Matter Alterations in PTSD. *Scientific Reports*. 2014; 6:33748 .DOI: 10.1038/srep33748

9.Shun Qi, Yunfeng Mu, Kang Liua, et al. Cortical inhibition deficits in recent onset PTSD after a single prolonged trauma exposure. *Neuroimage Clin.* 2013 Sep 3; 3:226-33. doi: 10.1016/j.nicl.2013.08.13

10. Chenn A, Walsh CA. Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science.* 2002;297(5580):365-9

11. 42. Pontious A, Kowalczyk T, Englund C, Hevner RF. Role of intermediate progenitor cells in cerebral cortex development. *Developmental Neuroscience*; 2008; 30(1-3):24-32

12. Cook F, Ciorciari J, Varker T, Devilly GJ. Changes in long term neural connectivity following psychological trauma. *Clinical Neurophysiology* 2009; 120: 309–314.

13. 78 Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Metzler TJ, Otte C et al. Delta sleep response to metyrapone in post-traumatic stress disorder. Neuropsychopharmacology 2003; 28: 1666–1676.

14. Otte C, Lenoci M, Metzler T, Yehuda R, Marmar CR, Neylan TC. Effects of metyrapone on hypothalamic-pituitary-adrenal axis and sleep in women with posttraumatic stress disorder. *Biological Psychiatry* 2007; 61: 952–956.

15. Bennett H, Wells A. Metacognition, memory disorganization and rumination in posttraumatic stress symptoms. *Journal of Anxiety Disorders* 2010; 24: 318–325.

16. Denson TF, Pedersen WC, Ronquillo J, Nandy AS. The angry brain: Neural correlates of anger, angry rumination, and aggressive personality. *Journal of Cognitive Neuroscience.* 2009; 21: 734–744.

17. Ferdek MA, van Rijn CM, Wyczesany M. Depressive rumination and the emotional control circuit: An EEG localization and effective connectivity study. *Cognitive Affect Behavioral Neuroscience* 2016; 16: 1099–1113.

18. Pape HC, Narayanan RT, Smid J, Stork O, Seidenbecher T. Theta activity in neurons and networks of the amygdala related to long-term fear memory. *Hippocampus* 2005; 15: 874–880.

19 Begić D, Hotujac L, Jokić-Begić N. Electroencephalographic comparison of veterans with combat-related post-traumatic stress disorder and healthy subjects. *Int J Psychophysiology* 2001; 40: 167–172.

20 Jokić-Begić N, Begić D. Quantitative electroencephalogram (qEEG) in combat veterans with post-traumatic stress disorder (PTSD). *Nordic Journal of Psychiatry* 2003; 57: 351–355.

21 Bader K, Schäfer V, Nissen L, Schenkel M. Heightened beta EEG activity during nonrapid eye movement sleep in primary insomnia patients with reports of childhood maltreatment. *J Clin Neurophysiology* 2013; 30: 188–198.

22 Hamner MB, Lorberbaum JP, George MS. Potential role of the anterior cingulate cortex in PTSD: review and hypothesis. *Depression and Anxiety* 1999; 9: 1–14.

23 Davis LL, Suris A, Lambert MT, Heimberg C, Petty F. Post-traumatic stress disorder and serotonin: new directions for research and treatment. *Journal of Psychiatry Neuroscience* 1997;22(5):318–326.

24 Celada, P., Puig, M.V., Martín-Ruiz, R. et al. Control of the Serotonergic System by the Medial Prefrontal Cortex. Potential Role in the Etiology of PTSD and Depressive Disorders. N*eurotoxicity Research* 2002; 4: 409. https://doi.org/10.1080/10298420290030550

25. Asnis GM, Kohn SR, Henderson M, Brown NL. SSRIs versus non-SSRIs in post-traumatic stress

disorder: an update with recommendations. *Drugs.* 2004;64(4):383-404.

26 Lynnette A.Averill, PreranaPurohit, Christopher L.Averill, et al. Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies. *Neuroscience Letters.*2017 May 10; Vol 649: 147-155

27 Ana Starcevic. Structural Brain Changes in PTSD http://dx.doi.org/10.5772/64080 (PTSD8)

28 Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NPV, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci.* 1998;1:69–73. doi:10.1038/271

29 Yehuda R, Bierer LM, Pratchett LC, Lehrner A, Koch EC, Van Manen JA, et al. Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: Randomized trial showing improved treatment retention and outcome. *Psychoneuroendocrinology*. 2015 Jan;51:589–597. doi:10.1016/j.psyneuen.2014.08.004

30 Starcevic A, Postic S, Radojicic Z, Starcevic B, Milovanovic S, Ilankovic A, et al. Volumetric analysis of amygdala, hippocampus, and prefrontal cortex in therapy-naive PTSD participants. *Biomed Res Int.* 2014;2014:968495.

31 Joëls M. Functional actions of corticosteroids in the hippocampus. *European Journal of Pharmacology.* 2008;583(2–3):312–321. doi:10.1016/j.ejphar.2007.11.064.

32 Bremner D. Does stress damage the brain? *Biological Psychiatry.* 1999;45(7):797–805. doi: 10.1016/S0006-3223(99)00009-8

33 Orcutt HK, King LA, King DW. Male-perpetrated violence among Vietnam veteran couples: relationships with veteran's early life characteristics, trauma history, and PTSD symptomatology. *Journal of Trauma Stress.* 2003;16(4):381–390. PMID: 12895021

34 Regan J, Barrett D, Gordon S. Childhood trauma and combat-related PTSD. *Tenn Med.* 2007;100(10):47–48. PMID: 17966719

35 Koenigs M, Huey ED, Raymont V, Cheon B, Solomon J, Wassermann EM, et al. Focal brain damage protects against post-traumatic stress disorder in combat veterans. *Nat Neuroscience.* 2008;11(2):232–237. doi:10.1038/nn2032

36 Stein MB, Hannah C, Koverola C, Yehuda R, Torchia M, McClarty B, et al. Neuroanatomical and neuroendocrine correlates in adulthood of severe sexual abuse in child-hood. Presented at the 33rd Annual Meeting, *American College of Neuropsychopharmacology;* December 1994; San Juan, puerto Rico.

37 Bremner JD, Randal P, Scot TM, Seibyl JP, Southwick SM, Delaney RC, et al. MRI-based measure of hippocampal volume in patients with PTSD. *American Journal of Psychiatry.* 1995;152:973– 981. doi:10.1176/ajp.152.7.973

38 Karl A, Schaefer M, Malta LS, Dörfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience Biobehav Rev.* 2006;30 (7):1004–1031.

PMID: 16730374

39 Han F, Xiao B, Wen L. Loss of glial cells of the hippocampus in a rat model of posttraumaticstress disorder. *Neurochem Res.* 2015;40(5):942–951. doi:10.1007/s11064-015-1549-6.

40 Golub Y, Kaltwasser SF, Mauch CP, Herrmann L, Schmidt U, Holsboer F, et al. Reduced hippocampus volume in the mouse model of Posttraumatic Stress Disorder. *J Psychiatry Res.* 2011;45(5):650–659. doi:10.1016/j.jpsychires.2010.10.014

41 LeDoux JE, Farb C, Ruggiero DA. Topographic organization of neurons in the acoustic thalamus that project to the amygdala. *Journal of Neuroscience.* 1990;10(4):1043–1054. doi:0270-6474/90/041043-1

42 Yehuda R, Halligan SL, Grossman R, Golier JA, Wong C. The cortisol and glucocorticoid receptor response to low dose dexamethasone administration in aging combat veterans and holocaust survivors with and without posttraumatic stress disorder. *Biological Psychiatry.* 2002;52(5):393–403. doi:10.1016/S0006-3223(02)01357-4

43 Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL Jr., Mason JW. Low urinary cortisol excretion in patients with posttraumatic stress disorder. *J Nerv Ment Dis* 1990;178(6):366–369. PMID: 2348190

44 Kim E Barrett, William F Ganong. Ganong's Review of Medical Physiology .New York, 2010; London by McGraw Hill Medical

45 Yehuda R, Kahana B, Binder-Brynes K, Southwick SM, Mason JW, Giller L. Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. *Am J Psychiatry*. 1995; 152(7):982–986. doi:10.1176/ajp.152.7.982

46 Kuljić B, Savić V, Černak I, Leposavić Lj, Milovanović S. Chronic stress procedure experimental model of depression or posttraumatic stress disorder (neuroendocrinological characteristics). *Psychatry.dan*. 1999;31(4):283–295. /2000/32/2-3/73-93/

47 Resnick H, Yehuda R, Pitman RK, Foy DW. Effect of previous trauma on acute plasma cortisol level following rape. *Am J Psychiatry.* 1995;152:1675–1677. doi:10.1176/ajp. 152.11.1675

48 Starcevic A, Postic S, Radojicic Z, Starcevic B, Milovanovic S, Ilankovic A, et al. Volumetric analysis of amygdala, hippocampus, and prefrontal cortex in therapy-naive PTSD participants. *Biomed Res Int.* 2014;2014:968495.

49 33] Rogers MA, Yamasue H, Abe O, Yamada H, Ohtani T, Iwanami A, et al. Smaller amygdala volume and reduced anterior cingulate gray matter density associated with the history of post-traumatic stress disorder. *Psychiatry Res.-Neuroimaging.*2009;174(3):210–216. doi:10.1016/j.pscychresns.2009.06.001

50 Weiss SJ. Neurobiological alterations associated with traumatic stress. *Perspect Psychiatr Care.* 2007 Jul;43(3):114–122. doi:10.1111/j.1744-6163.2007.00120.x

51 De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, et al. Brain structures in

pediatric maltreatment-related posttraumatic stress disorder: a socio demographically matched study. *Biological Psychiatry.* 2002;52:1066–1078. doi:10.1016/S0006-3223(02)01459-2

52 Doyère V, Debbie J, Monfils MH, Schaefer GE, LeDoux JE. Synapse-specific reconsolidation of distinct fear memories in the lateral amygdala. *Natural Neuroscience.* 2007 Apr;10(4): 414–416. PMID: 17351634

53 DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR. Testing predictions from personality neuroscience. Brain structure and the big five. *Psychol Sci.*2010;21(6):820–828. doi:10.1177/0956797610370159

54 Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, et al. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J Neurosci.* 2006;26(30):7870–7874. doi:10.1523/JNEUROSCI.1184-06.2006

55 Rajkowska G. Morphometric methods for studying the prefrontal cortex in suicide victims and psychiatric patients. *Ann NY Acad Sci.* 1997;836:253–268. doi:10.1111/j.1749-6632.1997.tb52364.x

56 Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. *Neurobiol. Aging.* 2014;35(2):S20–S28. doi:10.1016/j

57 Wang J, Korczykowksy M, Rao H, Fan Y, Pluta J, Gur RC et al. Gender diff erence in neural response to psychological stress. *Social Cogn Aff ect Neuroscience* 2008;2:227–239. doi: 10.1093/scan/nsm018

58 Reichel JM, Nissel S, Rogel-Salazar G, Mederer A, Käfer K, Bedenk BT, et al. Distinct behavioral consequences of short-term and prolonged GABAergic depletion in prefrontal cortex and dorsal hippocampus. *Front Behavioral Neuroscience.* 2015 Jan 13;8:452. doi:10.3389/fnbeh.2014.00452

59 Filipovic BR, Djurovic B, Marinkovic S, Stijak L, Aksic M, Nikolic V, Starcevic A, Radonjic V. Volume changes of corpus striatum, thalamus, hippocampus and lateral ventricles in posttraumatic stress disorder (PTSD) patients suffering from headaches and without therapy. *Cent Eur Neurosurg*. 2011;72(3):133–137. doi:10.1055/s-0030- 1253349

60 Goelman G, Ilinca R, Zohar, Weinstock M. Functional connectivity in prenatally stressed rats with and without maternal treatment with ladostigil, a brain-selective monoamine oxidase inhibitor. *European Journal of Neuroscience.* 2014;40(5):2734–2743. doi:10.1111/ejn. 12621.

61 Nofzinger EA, Buysse DJ, Miewald JM, et al. Human regional cerebral glucose metabolism during non rapid eye movement sleep in relation to waking. *Brain* 2002;125:1105– 1115. PMID: 11960899

62 Paulus MP, Stein MB, An Insular View of Anxiety. *Biological Psychiatry.* Volume 60, Issue 4, 15 August 2006, Pages 383-387. https://doi.org/10.1016/j.biopsych.2006.03.042

63. Paulus MP, Stein MB. Interoception in anxiety and depression. *Brain Structure and Function*.

2010;214(5-6):451–463. doi:10.1007/s00429-010-0258-9

64 Barrett LF, Simmons WK. Interoceptive predictions in the brain. *Nat Rev Neurosci*. 2015;16(7):419–429. doi:10.1038/nrn3950

65 Menon, V. & Uddin, L.Q. Saliency, switching, attention and control: a network model of insula function.*Brain Structure and Function* (2010) 214: 655. https://doi.org/10.1007/s00429-010-0262-0

66 Steven E.Bruceab, Katherine R.Buchholza, Wilson J.Browna, et al. Altered emotional interference processing in the amygdala and insula in women with Post-Traumatic Stress Disorder. *NeuroImage: Clinical.* Volume 2, 2013, Pages 43-49. https://doi.org/10.1016/j.nicl.2012.11.003

67 Ruth A.Laniusadf, Paul A.Frewenb, MurrayGirotti, et al. Neural correlates of trauma script-imagery in posttraumatic stress disorder with and without comorbid major depression: A functional MRI investigation *Psychiatry Research: Neuroimaging. 2007 May 15; 155(1):* 45-56 https://doi.org/10.1016/j.pscychresns.2006.11.006

68 R. J. L. Lindauer1,2,8 *, J. Booij3 , J. B. A. Habraken3 , et al. Effects of psychotherapy on regional cerebral blood flow during trauma imagery in patients with post-traumatic stress disorder: a randomized clinical trial. *Psychological Medicine* 2008; 38:543–554. f 2007 Cambridge University Press doi:10.1017/S0033291707001432

69 Alan N.Simmons, Martin P. Paulus, Steven R.Thorp, et al. Functional Activation and Neural Networks in Women with Posttraumatic Stress Disorder Related to Intimate Partner Violence *Biological Psychiatry.* 2008 Oct; 64(8): 681-690. https://doi.org/10.1016/j.biopsych.2008.05.027

70 Gregory A.Fonzoa, Alan N.Simmonsbde, Steven R.Thorpbd, et al. Exaggerated and Disconnected Insular-Amygdalar Blood Oxygenation Level-Dependent Response to Threat-Related Emotional Faces in Women with Intimate-Partner Violence Posttraumatic Stress Disorder. *Biological Psychiatry;* 2010 Sep; 68(5): 433-441

71 Baker, L.M., Williams, L.M., Korgaonkar, M.S. et al. Impact of early vs. late childhood early life stress on brain morphometrics. *Brain Imaging and Behavior* 2013;7: 196. https://doi.org/10.1007/s11682-012-9215-y

72 Kathryn L.Loveroab, Alan N.Simmonsab, Jennifer L.Arona, Martin P.Paulusab, Anterior insular cortex anticipates impending stimulus significance. *NeuroImage.* 2009 Apr; 45(3): 976-983. https://doi.org/10.1016/j.neuroimage.2008.12.070
|
73 Craig, A. D.; Craig, A D Bud. How do you feel--now? The anterior insula and human awareness. *Nature Reviews Neuroscience*. 2009 Jan, 10(1): 59-70.

74 Noriyuki Kitayam, SineadQuinn, J. DouglasBremner, Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *Journal of Affective Disorders.* 2006 Feb; 90(2-3): 171-174. https://doi.org/10.1016/j.jad.2005.11.006

75 Mark B Hamner M.D., Jeffrey P. Lorberbaum M.D., Mark S. George M.D. Potential role of the anterior cingulate cortex in PTSD: Review and hypothesis. *Depression and Anxiety* 9:1–14, 199. https://doi.org/10.1002/(SICI)1520-6394(1999)9:1

76 Michael DDe Bellis, Matcheri Skeshavan, KarinFrustaci, et al. Superior temporal gyrus volumes in maltreated children and adolescents with ptsd. *Biological Psychiatry.* 2002 Apr 1; 51(7): 544-552. https://doi.org/10.1016/S0006-3223(01)01374-9

77 Sophie E. Holmes, Dustin Scheinost, Nicole DellaGioia, et al. Cerebellar and Prefrontal Cortical Alterations in PTSD: Structural and Functional Evidence. Chronic Stress. 2018; Vol 2: 1–11. DOI: 10.1177/2470547018786390

78 Botez Cerebellum MI, Ramachandran VS. (Ed.), *Encyclopedia of Human Behavior*, New York: Academic Press, 1999: p. 2002.

79 Schmahmann JD, Caplan D. Cognition, emotion and the cerebellum. *Brain* 2006; 129: 290–292.

80 Schutter DJ, Van Honk J. The cerebellum on the rise in human emotion. *Cerebellum* 2005; 4: 290–294.

81 Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron* 2013; 80: 807–815.

82 Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum—insights from the clinic. *Cerebellum*. 2007; 6: 254–267.

83 De Bellis MD, Kuchibhatla M. Cerebellar volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biological Psychiatry* 2006; 60: 697–703.

84 Baldac¸ara L, Jackowski AP, Schoedl A, et al. Reduced cerebellar left hemisphere and vermal volume in adults with PTSD from a community sample. *J Psychiatr Res* 2011; 45: 1627–1633.

85 DiGangi JA, Tadayyon A, Fitzgerald DA, et al. Reduced default mode network connectivity following combat trauma. *Neuroscience Letters* 2016; 615: 37–43.

86 Lanius R, Bluhm R, Coupland N, et al. Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. *Acta Psychiatr Scand* 2010; 121: 33–40.

87 Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry* 2007; 164: 1476–1488.

88 Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network. *Ann N Y Acad Sci* 2008; 1124: 1–38.

89 Lanius RA, Vermetten E, Loewenstein RJ, et al. Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. *Am J Psychiatry* 2010; 167: 640–647.

90 Hayes JP, VanElzakker MB, Shin LM. Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. *Front Integr Neurosci* 2012; 6: 89.

91 Hayes JP, VanElzakker MB, Shin LM. Emotion and cognition interactions in PTSD: a review of

neurocognitive and neuroimaging studies. *Front Integr Neurosci* 2012; 6: 89.

92 Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT. The organization of the human estimated by intrinsic functional connectivity. *Journal of Neurophysiology* 2011; 106: 2322–2345.

93 Bluhm RL, Williamson PC, Osuch EA, et al. Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *Journal of Psychiatric Neuroscience* 2009; 34: 187–194.

94 Sripada RK, King AP, Welsh RC, et al. Neural dysregulation in posttraumatic stress disorder: evidence for disrupted equilibrium between salience and default mode brain networks. *Psychosomatic Medicine* 2012; 4: 904–911.

95 Grant, S., Colaiaco, B., Motala, A., et al. *Needle Acupuncture for Posttraumatic Stress Disorder (PTSD): A Systematic Review.* Santa Monica, CA: RAND Corporation, 2017. Web. <https://www.rand.org/pubs/research_reports/RR1433.html.>

96 Kim, Y.-D. et al. Acupuncture for posttraumatic stress disorder: a systematic review of randomized controlled trials and prospective clinical trials. *Evidence-based Complementary and Alternative Medicine : eCAM.* 2013 2013;: 615857. *PMC*. Web. 17 Oct. 2017.

97 Hollifield, M.,Nityamo, S.-L., Warner, T., Hammerschlag, R. Acupuncture for Posttraumatic Stress Disorder: A Randomized Controlled Pilot Trial. *Journal of Nervous & Mental Disease.* 2007 Jun; 195(6) : 504-513. doi: 10.1097/NMD.0b013e31803044f8

98 7. Engel C.-C., Cordova, E.-H., Benedek, D.-M., et al. Randomized effectiveness trial of a brief course of acupuncture for posttraumatic stress disorder. *Medical Care.* 2014 Dec; 52 (12 Suppl 5) : S57-64. doi: 10.1097/MLR.0000000000000237.

99 Wang, Y., Hu, Y.-P., Wang, W.-C., Pang, R.-Z., Zhang, A.-R. Clinical studies on treatment of earthquake-caused posttraumatic stress disorder using electroacupuncture. *Evidence-Based Complementary and Alternative Medicine.* 2012 2012: 7 pages. Article ID 431279. doi:10.1155/2012/431279

100 Li QQ, Shi GX, Xu Q, Wang J, Liu CZ, Wang LP. Acupuncture effect and central autonomic regulation. *Evidence Based Complementary and Alternative Medicine*. 2013;2013:267959. doi:10.1155/2013/267959

101 Li P, Longhurst JC. Neural mechanism of electroacupuncture's hypotensive effects. Autonomic *Neuroscience.* 2010;157(1-2):24–30.

102 Zhou W, Longhurst JC. Neuroendocrine mechanisms of acupuncture in the treatment of hypertension. *Evidence-Based Complementary and Alternative Medicine*. 2012;2012:9 pages.878673

103 Chen J, Song GQ, Yin J, Koothan T, Chen JDZ. Electroacupuncture improves impaired gastric motility and slow waves induced by rectal distension in dogs. *The American Journal of Physiology*. 2008;295(3):G614–G620.

104 Ouyang H, Xing J, Chen J. Electroacupuncture restores impaired gastric accommodation in

vagotomized dogs. *Digestive Diseases and Sciences.* 2004;49(9):1418–1424.

105 Guo ZL, Longhurst JC. Expression of c-Fos in arcuate nucleus induced by electroacupuncture: relations to neurons containing opioids and glutamate. *Brain Research.* 2007;1166(1):65–76.

106 Guo ZL, Moazzami AR, Tjen-A-Looi S, Longhurst JC. Responses of opioid and serotonin containing medullary raphe neurons to electroacupuncture. *Brain Research.* 2008;1229:125–136.

107 Li M, Tjen-A-Looi SC, Longhurst JC. Electroacupuncture enhances preproenkephalin mRNA expression in rostral ventrolateral medulla of rats. *Neuroscience Letters.* 2010;477(2):61–65.

108 Boyadjieva N, Advis JP, Sarkar DK. Role of β-endorphin, corticotropin-releasing hormone, and autonomic nervous system in mediation of the effect of chronic ethanol on natural killer cell cytolytic activity. *Alcoholism: Clinical and Experimental Research.* 2006;30(10):1761–1767.

109 Harbach H, Moll B, Boedeker RH, et al. Minimal immunoreactive plasma β-endorphin and decrease of cortisol at standard analgesia or different acupuncture techniques. *European Journal of Anaesthesiology*. 2007;24(4):370–376.

110 Wingate, Douglas S. *Healing Brain Injury with Chinese Medical Approaches: Integrative Approaches for Practitioners*. Singing Dragon, 2018.

111 Tomé D, Schwarz J, Darcel N, Fromentin G. Protein, amino acids, vagus nerve signaling, and the brain. *The American Journal of Clinical Nutrition*. 2009;90(3):838S–843S.

112 Noh J, Seal RP, Garver JA, Edwards RH, Kandler K. Glutamate co-release at GABA/glycinergic synapses is crucial for the refinement of an inhibitory map. *Nature Neuroscience.* 2010;13(2):232–238.

113 Seal RP, Wang X, Guan Y, et al. Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. *Nature.* 2009;462(7273):651–655.

114 Ishide T, Amer A, Maher TJ, Ally A. Nitric oxide within periaqueductal gray modulates glutamatergic neurotransmission and cardiovascular responses during mechanical and thermal stimuli. *Neuroscience Research*. 2005;51(1):93–103.

115 Guo ZL, Longhurst JC. Activation of reciprocal pathways between arcuate nucleus and ventrolateral periaqueductal gray during electroacupuncture: involvement of VGLUT3. *Brain Research.* 2010;1360:77–88

116 Tjen-A-Looi SC, Li P, Longhurst JC. Role of medullary GABA, opioids, and nociceptin in prolonged inhibition of cardiovascular sympathoexcitatory reflexes during electroacupuncture in cats. *The American Journal of Physiology.* 2007;293(6):H3627–H3635.

117 Manni L, Albanesi M, Guaragna M, Paparo SB, Aloe L. Neurotrophins and acupuncture. *Autonomic Neuroscience.* 2010;157(1-2):9–17.

118 Mannerås L, Jonsdottir IH, Holmäng A, Lönn M, Stener-Victorin E. Low-frequency electro-acupuncture and physical exercise improve metabolic disturbances and modulate gene expression in adipose tissue in rats with dihydrotestosterone-induced polycystic ovary syndrome. *Endocrinology.*

2008; 149(7):3559–3568.

119 Mannerås L, Cajander S, Lönn M, Stener-Victorin E. Acupuncture and exercise restore adipose tissue expression of sympathetic markers and improve ovarian morphology in rats with dihydrotestosterone-induced PCOS. *The American Journal of Physiology.* 2009;296(4):R1124–R1131.

120 Mani L, Roco ML, Paparo SB, Guaragna M. Electroacupucture and nerve growth factor: potential clinical applications. *Archives Italiennes de Biologie.* 2011;149(2):247–255.

121 Noguchi E. Acupuncture regulates gut motility and secretion via nerve reflexes. *Autonomic Neuroscience.* 2010;156(1-2):15–18.

122 Macefield VG, Henderson LA. Real-time imaging of the medullary circuitry involved in the generation of spontaneous muscle sympathetic nerve activity in awake subjects. *Human Brain Mapping.* 2010;31(4):539–549.

123 Napadow V, Dhond R, Conti G, Makris N, Brown EN, Barbieri R. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. *NeuroImage*. 2008;42(1):169–177.

124 Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine.* 2009;37(2):141–153.

125 Burnstock G. Acupuncture: a novel hypothesis for the involvement of purinergic signalling. *Medical Hypotheses*. 2009;73(4):470–472.

126 Frahm KA, Schow MJ, Tobet SA. The vasculature within the paraventricular nucleus of the hypothalamus in mice varies as a function of development, subnuclear location, and GABA signaling. *Hormone and Metabolic Research.* 2012;44(8):619–624.

127 Nunn N, Womack M, Dart C, Barrett-Jolley R. Function and pharmacology of spinally-projecting sympathetic pre-autonomic neurones in the paraventricular nucleus of the hypothalamus. *Current Neuropharmacology*. 2011;9(2):262–277.

128 Eshkevari L, Permaul E, Mulroney SE. Acupuncture blocks cold stress-induced increases in the hypothalamus-pituitary-adrenal axis in the rat. *Journal of Endocrinology.* 2013;217(1):95–11

129 Eshkevari L, Egan R, Phillips D, et al. Acupuncture at ST36 prevents chronic stress-induced increases in neuropeptide Y in rat. *Experimental Biology and Medicine.* 2012;237(1):18–23.

130 Li P, Tjen-A-Looi SC, Longhurst JC. Nucleus raphé pallidus participates in midbrain-medullary cardiovascular sympathoinhibition during electroacupuncture. *The American Journal of Physiology.* 2010;299(5):R1369–R1376.

131 Tjen-A-Looi SC, Li P, Longhurst JC. Midbrain vlPAG inhibits rVLM cardiovascular sympathoexcitatory responses during electroacupuncture. *The American Journal of Physiology.* 2006;290(6):H2543–H2553.

132 Wang J, Irnaten M, Neff RA, et al. Synaptic and neurotransmitter activation of cardiac vagal

neurons in the nucleus ambiguus. *Annals of the New York Academy of Sciences.* 2001;940:237–246.

133 Guo ZL, Li M, Longhurst JC. Nucleus ambiguus cholinergic neurons activated by acupuncture: relation to enkephalin. *Brain Research.* 2012;1442:25–35.

134 Tjen-A-Looi SC, Li P, Longhurst JC. Processing cardiovascular information in the vlPAG during electroacupuncture in rats: roles of endocannabinoids and GABA. *Journal of Applied Physiology.* 2009;106(6):1793–1799.

135 Li P, Tjen-A-Looi SC, Guo ZL, Longhurst JC. An arcuate-ventrolateral periaqueductal gray reciprocal circuit participates in electroacupuncture cardiovascular inhibition. *Autonomic Neuroscience.* 2010;158(1-2):13–23.

136 Buijs RM, van Eden CG. The integration of stress by the hypothalamus, amygdala and prefrontal cortex: balance between the autonomic nervous system and the neuroendocrine system. *Progress in Brain Research.* 2000;126:117–132.

137 Tanida M, Katsuyama M, Sakatani K. Effects of fragrance administration on stress-induced prefrontal cortex activity and sebum secretion in the facial skin. *Neuroscience Letters.* 2008; 432(2): 157–161.

138 passatore M, Roatta S. Influence of sympathetic nervous system on sensorimotor function: whiplash associated disorders (WAD) as a model. *European Journal of Applied Physiology.* 2006; 98(5):423–449.

139 Xin-Yan Gaoab, Shi-Ping Zhanga, Bing, Zhub, Hong-Qi Zhang, Investigation of specificity of auricular acupuncture points in regulation of autonomic function in anesthetized rats. *Autonomic Neuroscience*. 2008 Feb, 138(1-2):50-56. https://doi.org/10.1016/j.autneu.2007.10.003

140 Xin-Yan Gao, Lu Wang, Ingrid Gaischek, Yvonne Michenthaler, Bing Zhu, and Gerhard Litscher, "Brain-Modulated Effects of Auricular Acupressure on the Regulation of Autonomic Function in Healthy Volunteers," *Evidence-Based Complementary and Alternative Medicine*, 2012; vol. 2012, Article ID 714391, 8 pages. https://doi.org/10.1155/2012/714391.

141 Wei He, Xiaoyu Wang, Hong Shi, et al., "Auricular Acupuncture and Vagal Regulation," *Evidence-Based Complementary and Alternative Medicine*, 2012; vol. 2012, Article ID 786839, 6 pages. https://doi.org/10.1155/2012/786839.

142 Wei He, Pei-Jing Rong, Liang Li, Hui Ben, Bing Zhu, and Gerhard Litscher, "Auricular Acupuncture May Suppress Epileptic Seizures via Activating the Parasympathetic Nervous System: A Hypothesis Based on Innovative Methods," *Evidence-Based Complementary and Alternative Medicine,* 2012; vol. 2012, Article ID 615476. https://doi.org/10.1155/2012/615476.

143 Huang W, Pach D, Napadow V, et al. Characterizing Acupuncture Stimuli Using Brain Imagining with fMRI – A Systematic Review and Meta-Analysis of the Literature. *PloS ONE* 7(4):e32960. doi:10.1371/journal.pone.0032960

144 Tan TT, Wang D, Huang JK, et al. Modulatory effects of acupuncture on brain networks in mild cognitive impairment patients. *Neural Regen Res*. 2017;12(2):250–258. doi:10.4103/1673-

5374.200808

145 Kathleen K.S., Huia Jing, Liua Ovid, et al. The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36 as evidenced by fMRI. *NeuroImage* 2005; 27(3): 479-496. https://doi.org/10.1016/j.neuroimage.2005.04.037

146 Wei Qin, Jie Tian, Lijun Bai, et al. FMRI connectivity analysis of acupuncture effects on an amygdala-associated brain network. *Molecular Pain* 2008, 4:55 doi:10.1186/1744-8069-4-55

147 Hui KK1, Liu J, Makris N, et al. Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects. *Human Brain Mapping.* 2000;9(1):13-25.

148 Bao Chunhui, Wang Di, Liu Peng, et al. Effect of Electro-Acupuncture and Moxibustion on Brain Connectivity in Patients with Crohn's Disease: A Resting-State fMRI Study. *Frontiers in Human Neuroscience*. (2017) 11: 559. DOI=10.3389/fnhum.2017.00559

149 Wang X, Wang Z, Liu J, et al. Repeated acupuncture treatments modulate amygdala resting state functional connectivity of depressive patients. *Neuroimage Clin*. 2016;12:746–752. Published 2016 Jul 27. doi:10.1016/j.nicl.2016.07.011

150 Joshua D. Claunch, Suk-Tak Chan, Erika E. Nixon, et al.Commonality and Specificity of Acupuncture Action at Three Acupoints as Evidenced by fMRI *The American Journal of Chinese Medicine* 2012; 40(04): 695-712. https://doi.org/10.1142/S0192415X12500528

151 Huang, Wenjing & Pach, Daniel & Napadow, Vitaly & Park, et al. Characterizing Acupuncture Stimuli Using Brain Imaging with fMRI - A Systematic Review and Meta-Analysis of the Literature. *PloS one.* 2012; 7. e32960. 10.1371/journal.pone.0032960.

152 Wang Z, Liang P, Zhao Z, et al. Acupuncture modulates resting state hippocampal functional connectivity in Alzheimer disease. *PLoS One*. 2014;9(3):e91160. Published 2014 Mar 6. doi:10.1371/journal.pone.0091160

153 Claunch JD, Chan ST, Nixon EE, et al. Commonality and specificity of acupuncture action at three acupoints as evidenced by FMRI. *American Journal of Chinese Medicine* 2012;40(4):695–712. doi:10.1142/S0192415X12500528

154 Wu H, Kan H, Li C, et al. Effect of Acupuncture on Functional Connectivity of Anterior Cingulate Cortex for Bell's Palsy Patients with Different Clinical Duration. *Evidence Based Complementary and Alternative Medicine* 2015;2015:646872. doi:10.1155/2015/646872

155 Min-Ho Nam, Chang Shik Yin, Kwang-Sup Soh, Seung-hoon Choi, Adult Neurogenesis and Acupuncture Stimulation at ST36. *Journal of Acupuncture and Meridian Studies,* 2011;4(3): 153-158. https://doi.org/10.1016/j.jams.2011.09.001.

156 Min-HoNam*Kwang SeokAhn*Seung-HoonChoi, Chapter Four - Acupuncture Stimulation Induces Neurogenesis in Adult Brain. *International Review of Neurobiology* 2013; Volume 111, Pp 67-90. https://doi.org/10.1016/B978-0-12-411545-3.00004-3