Acupuncture Approaches to Borderline Personality Disorder: A Neurobiological Approach

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Borderline Personality Disorder (BPD) is a relatively recently recognized and studied condition that is continuing to unfold in terms of definition, understanding, and treatment approaches. The national prevalence in the United States estimates 0.7-3.5% of the population being affected.[1-4] Related impairments in the realms of emotional and impulse regulation, identity, and interpersonal relationships can cause major problems in social adaptation[5] and quality of life[6].

Due to individuals with BPD frequently partaking in self-harming behavior and suicide attempts[7], low patient compliance[8], and negative life-style and health related behaviors[9], patients with BPD often experience considerable medical co-morbidities and can be regarded to be "difficult" to treat. They may actively challenge the health care provider's interpersonal skills, take additional time, become non-compliant, or may have a higher tendency to drop out of treatment.[10] It may be for these reasons that it is a matter infrequently discussed in the realm of acupuncture approaches and what may be offered to the patient.

This paper will explore key information about diagnostics, current neurophysiological findings, and treatment considerations based on these findings. The possible role of early life trauma as a predisposing factor to the development of BPD and commonalities with Post-traumatic Stress Disorder (PTSD) and Complex Post-traumatic Stress Disorder (C-PTSD) will also be discussed.

Diagnostic criteria for BPD

The Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition; DSM-5)[11] contains two diagnostic approaches, a categorical one and a hybrid dimensional model consisting of personality functioning (PF) and personality traits. The primary approach of the DSM-5, section II, consists of criteria that have to be met for a personality disorder diagnosis. General criteria refer to domains of the personality affected, inflexibility, distress, and chronicity of the condition. Specific diagnostic criteria of BPD are given in Table 1. The diagnosis of BPD is generally made clinically by experienced specialists; however the use of psychological tests such as the Personality Disorder Questionaire-4+[12, 13] or the Assessment of DSM-5 personality Disorders[14] can be helpful. The Borderline Symptom List[15] can be used to evaluate changes in symptoms.

Table 1: Diagnostic Criteria of BPD according to DSM-5, section II, page 663[11] ***A pervasive pattern of instability of interpersonal relationships, self-image, and effects and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:***
1) Frantic efforts to avoid real or imagined abandonment
2) A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
3) Identity disturbance: markedly and persistently unstable self-image or sense of self
4) Impulsivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating)
5) Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior
6) Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
7) Chronic feelings of emptiness
8) Inappropriate, intense anger or difficulty controlling anger (e.g frequent displays of temper, constant anger, recurrent physical fights)
9) Transient, stress-related paranoid ideation or severe dissociative symptoms

The Alternative DSM-5 Model of Personality Disorders (AMPD) comprises five personality disorder trait domains with a certain number of facets each. These domains are:

1) negative affectivity
2) detachment
3) antagonism
4) disinhibition
5) psychoticism
Components of these domains are laid out below in Table 2.

Table 2: Proposed diagnostic criteria of BPD according to DSM-5, section III, page 766-67 [11]
Moderate or greater impairment in personality functioning, manifested by characteristic difficulties in two or more of the following four areas
1) IDENTITY: markedly impoverished, poorly developed, or unstable self-image, often associated with excessive self-criticism; chronic feelings of emptiness; dissociative states under stress 2)SELF-DIRECTION: instability of goals, aspirations, values, or career plans 3)EMPATHY: compromised ability to recognize the feelings or needs of others associated with interpersonal hypersensitivity (i.e. prone to feel slighted or insulted); perceptions of others selectively biased toward negative attributes or vulnerabilities 4) INTIMACY: intense, unstable, and conflicted close relationships, marked by mistrust, neediness, and anxious preoccupation with real or imagined abandonment; close relationships often viewed in extremes of idealization and devaluation and alternating between over-involvement and withdrawal
Four or more of the following seven personality traits, at least one of which must be (5) impulsivity, (6) risk taking, or (7) hostility:
1) EMOTIONAL LABILITY (an aspect of negative affectivity): Unstable emotional experiences and frequent mood changes; emotions that are easily aroused, intense, and/or out of proportion to events and circumstances 2) ANXIOUSNESS (an aspect of negative affectivity): intense feelings of nervousness, tenseness, or panic, often in reaction to interpersonal stresses; worry about the negative effects of past unpleasant experiences and future negative possibilities; feeling fearful, apprehensive, or threatened by uncertainty; fears of feeling apart or losing control 3) SEPARATION INSECURITY(an aspect of negative affectivity): fears of rejection by- and/or separation from – significant others, associated with fears of excessive dependency and complete loss of autonomy 4) DEPRESSIVITY (an aspect of negative affectivity): frequent feelings of being down, miserable, and/or hopeless; difficulty recovering from such moods; pessimism about the future; pervasive shame; feelings of inferior self-worth; thoughts of suicide and suicidal behavior 5) IMPULSIVITY (an aspect of disinhibition): acting in the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing or following plans; a sense of urgency and self-harming behavior under emotional stress 6) RISK TAKING (and aspect of disinhibition): engagement in dangerous, risky, and potentially self-damaging activities, unnecessarily and without regard to consequences; lack of concern for one's limitations and denial of the reality of personal danger 7) HOSTILITY (an aspect of antagonism): Persistent or angry feelings; anger or irritability in response to minor slights and insults

Physical changes to cortical structures, including connectivity, activation intensity, and tissue volume loss have been demonstrated to correlate with BPD and will be explored below.

Borderline Personality Disorder versus Post-Traumatic Stress Disorder

Many symptoms that present in cases of BPD have similarities to, or overlap with PTSD, particularly cases of “complex PTSD” or “C-PTSD”. Some have argued that BPD and PTSD may actually be “two sides of the same coin” with age of trauma being a key differentiating factor,[16] claiming that trauma sustained during early childhood would favor the development of BPD while trauma in adulthood would tend to develop into PTSD symptomology. Overlaps between these two conditions are demonstrated in Table 3 below.

Levels of comparison	***Shared features between BPD and PTSD***

Etiological level	-High frequency of trauma -Evidences for gene-environment interaction [17,18]
Clinical level	Major disturbances in:[19,20] -Emotional regulation -Impulse control -Reality testing -Interpersonal relationships -Sense of identity
Neurofunctional level	-Abnormalities in frontolimbic networks [21,22] -Limbic hyperactivity and diminished recruitment of frontal brain regions
Neurobiological level	Hypothalamus-pituitary-adrenal (HPA) axis dysregulation [23, 24]
Genetic level	Association with FKBP5 [17, 25]

Variances in ICD-11 diagnostic criteria has been pointed out[26] (see Table 4) with distinguishing factors between PTSD and C-PTSD being chronic and repeated traumas alongside additional disturbances in self-organization e.g. emotion regulation, self-concept, and relational difficulties.[27] Despite it's high occurrence rate in BPD, a principle difference between it and C-PTSD is that BPD does not include trauma as a necessity within it's diagnostic criteria. It is instead distinguished by 1) frantic efforts to avoid real or imagined abandonment, 2) shifting self-image or self-concept (“feeling empty”), 3) shifting idealization and devaluation in relationships, and 4) frequent impulsiveness often including self-harm or suicidal behaviors. It is noted that in cases of C-PTSD self-identity has been found to be consistently negative as opposed to the shifting nature of BPD, and relational dynamics tend to be chronic avoidance of relationships in C-PTSD rather than sustained chaotic engagement found in BPD.

Diagnostic symptomology for PTSD, C-PTSD, and BPD[26]		
ICD-11 PTSD	*ICD-11 C-PTSD*	*DSM-IV BPD*
Re-experiencing -Flashbacks, nightmares	Re-experiencing -Flashbacks, nightmares	
Avoidance -Thoughts, people, places, activities	Avoidance -Thoughts, people, places, activities	
Sense of threat -Hypervigilance, startle	Sense of threat -Hypervigilance, startle	
	Interpersonal problems -Not close, feeling disconnected	
	Negative self-concept -Worthlessness, guilt	
	Emotion Regulation -Anger, hurt feelings	Emotion Regulation -Anger, hurt feelings
		Frantic unstable relationships
		Unstable sense of self
		Impulsiveness
		Self-harm
		Mood changes
		Chronic feeling of emptiness
		Dissociation

PTSD symptoms of dissociative amnesia and flashbacks, emotional numbing, and anger have similar features to those of transient dissociation, chronic emptiness, and chronic anger, respectively, found in BPD. This becomes even more troublesome in differentiation as DSM-5's[11] revised PTSD criteria include new symptoms reflecting pervasive negative changes in affect, identity, and behavior which overlap with four BPD criteria – identity disturbance, potentially self-damaging impulsivity, self-harm, affect instability. This places PTSD with a potential overlap of seven of nine criteria of BPD.

The hypothesis of age-dependency is supported by evidence demonstrating that neuroplasticity and neurological impacts of trauma will vary in severity and symptomology based on age of trauma exposure.[29,16] In rat studies it has been shown that injuries experienced earlier in life generally had a worse effect, with those sustained within the first few days of life having "dramatically different behavioral and anatomical outcomes" compared to injuries sustained only a couple weeks later. This sparing found in the later injuries showed nearly normal cognitive test results with only partial motor recovery while both factors were significantly impacted with early life injuries.[30] The concept of the stress axis having varying windows of regulation following trauma is well known.[31]

The prevalence of early childhood trauma is so frequently associated with BPD that a causal relationship has been suggested.[32,33] This includes neglect (92%), sexual abuse (40-70%), or physical abuse (25-73%).[34] Sexual abuse has been found to the most significant predictor of the diagnosis of both borderline personality disorder and C-PTSD, with intrafamilial sexual abuse alone increasing the odds of meeting criteria for both by 26%.Those reporting early-onset of abuse reported higher intrafamilial rates, lack of single incidents of abuse, higher lifetime revictimization, and higher biparental neglect.[35]

The core features of dysphoria felt in BPD revolve around a terror of abandonment or rejection, and alternating idealization and devaluation of others.[28] This is consistent with laboratory research findings in which those meeting BPD criteria responded strongest to scripts highlighting themes of abandonment, while those meeting PTSD but not BPD responded strongest to those scripts of traumatic (e.g. violent, abusive, life-threatening) events.[36] Similarly, hypervigilance found in C-PTSD tends to relate to avoidance of being harmed, while in BPD it seems more apt to involve extreme sensitivity (which can take the form of hypervigilance) to perceiving oneself as being abandoned or rejected.[37] Emotional regulation is known to be founded on developmental attainments (e.g. emotion self-awareness, empathy, self-control) that are greatly influenced by one's interactions with primary caregivers beginning in infancy and into childhood.[38] Affect dysregulation has correspondingly been found to be associated with childhood relationships with primary caregivers who are unresponsive, poorly attuned, or punitive.[39] Individuals with BPD often report histories of childhood neglect, abuse, invalidation, or impairment on the part of the primary caregiver.[40,41]

In light of this it has been put forth that the emotional pain that seems part of the "essential nature" of BPD[42] could either be due to traumatic victimization in childhood or adulthood, or may alternately develop when a child experiences disruptions in formative relationships with primary caregiver(s) that lead to either abandonment or rejection.[43,44]

FKBP5 is an important genetic regulator of the glucocorticoid receptor complex and has been associated with PTSD in numerous studies[17] and has more recently been shown to correlate with BPD diagnosis as well,[25,29] pointing to a shared genetic vulnerability. The impacts on the cortisol regulation system in PTSD, notably markedly low basal cortisol levels with increased receptor density and sensitivity has been documented[45] and explored previously by this author.[46] Patients with BPD conversely have demonstrated elevated continuous cortisol output with blunted cortisol following

psychosocial challenges.[47,48] A 2015 study showed that trauma exposure in children after the age of 1 year old related to diverging diurnal cortisol slopes regardless of gender while trauma exposure before the age of 1 year showed delayed recovery from peak responses to physiological stress.[49]

Common comobidities with Borderline Personality Disorder

Monomorbid BPD patients – patients who present without any significant comorbitity -are considered a relative rarity.[50] Comorbid mood disorders are very common, occurring in 50-60% of all BPD patients.[51,52] Anxiety disorders (including PTSD) have been found in 60-80% of individuals.[52,53] Substance use disorders have been reported in slightly greater than 50% of BPD patients.[52,54] Eating disorders also frequently occur with anorexia nervosa found in 7-21% and bulemia nervosa found in 13-31% of all BPD patients.[54,55,56] This is more prevalent than many other DSM domains.[57] Looking at it from the other direction, BPD has been found as a comorbid condition in 50% of eating disorder diagnoses.[28]

In addition to psychiatric disorders, it is well known the BPD considerately increases the risk of a number of medical (somatic) conditions as well.[50] Additionally BPD can complicate the course of several diseases[58] which can be attributed in part to poor health-related behavior and lifestyle.[50] Patients with BPD may show poor adherence to psychological and medical treatment recommendations[59] and may sabotage their medical treatment.[60,61] As a result BPD is associated with cardiovascular (15.3%), gastrointestinal (21.1%), and hepatic disease (3.1%). It is additionally correlated with pain conditions like arthritis (17.2-27.7%) and chronic pain in general (62.5-80.3%).[62]

Interoception in Borderline Personality Disorder

Interoception is defined as the sensing of internal physiological states of the body such as hunger, micturition, thirst, temperature, etc which acts as a means of regulating and maintaining homeostasis.[63] This is a central processing of bottom-up visceral-afferent signals from the body by the central nervous system through autonomic pathways[64] along with top down regulatory directives which may or may not be experienced as subjective feelings. These feelings can then lead to behaviors to adjust the state.[65]

The vagus nerve contains about 80-85% of afferent fibers that project the the solitary tract (NTS) and further the brain stem and subcortical regions including the hypothalamus and amygdala.[66] It is now widely accepted that there is a distributed central interoceptive system including the brainstem, thalamus, insula, somatosensory, and cingulate cortices[63;] and particularly relevant to this discussion, the anterior insular cortex, especially in the right hemisphere.[67] Afferent baroreceptors in the heart and their vessels are responsible for cardiovascular regulation such as visceral sensations and concomitant feelings.[66] These signals are not always conscious, but they may reach consciousness under circumstances if a homeostatic threshold is exceeded or if attention is guided towards a certain body process needing to be evaluated and integrated with psychological processes.[64,68] This sense is functionally distinct from exteroceptive senses such as vision or hearing as well as separate from proprioception, which is the sensing of the position of muscles and joints. Interoception does however interact with these other senses through multimodal sensory integration.[69]

Interoception is often conceptualized into three distinct processes:
Interoceptive Accuracy: one's ability to perceive their own bodily signals in behavioral tasks
Interoceptive Sensibility: one's tendency to focus on internal signals which may be captured on self-reporting questionnaires.
Interoceptive Awareness: one's metacognitive judgment on interoceptive accuracy and an individual's confidence ratings predicting their actual interoceptive accuracy[67]

More recently a fourth process, the visceral-afferent signal transmission and representation, has been added to define objective physiological states.[70]

Recent theoretical works have proposed disturbed interoception as a type of "p-factor' or general factor underlying psychopathology.[71,72] Findings have indicated that BPD is associated with impaired representation of afferent interoceptive signals[73] with a tight link between interoception and reduced emotional awareness,[74] a distinct feature found in BPD.[75]

It has been hypothesized that the risk for development of BPD is increased when a child grows up in a social environment characterized by a high degree of perceived intolerance for the individual's emotional expression.[76,77] It is possible that this inadequate emotional feedback can result in reduced emotional awareness in terms of an inability to identify, understand, and label one's own emotional responses. This results in deficits in the ability to regulate one's own emotions.[78] It has also been assumed that consistent early life adversities (ELA) may lead to a stronger focus on external stimuli as a natural protective strategy to prevent or be prepared for further potentially harmful events, setting the ground for interpersonal hypersensitivity in social situations[79] while paying little attention to their own inner processes, feelings, and needs. This alongside invalidation from caregivers contribute to emotional disregulation. If children do not learn to connect their own emotions with physical reactions and if the child's emotions, needs, and physiological signals are constantly being ignored, invalidated, or punished, the internal signals receive less and less attention.[80] Emotional experiences become associated more with external than internal cues and the ability to regulate emotions remain poor due to lack of parental guidance.[81]

There has been evidence that acute and chronic stress, including ELAs negatively affect interoception.[82] Early life stress may cause chronic overactivation of the physiological brain-body axis, which in turn induces impaired function of the underlying bi-directional circuits, resulting in disturbed interoception.[64] During traumatic situations dissociative states and processes are often adaptive in nature, offering some relief during victimization; however continuous post-trauma dissociation can be very disruptive and further disconnect individuals from bodily awareness.[83] Challenging social situations lead to an acute switch from interoceptive to exteroceptive attention.[65] This deficit in interoceptive signaling may also enhance emotional sensitivity to social exclusion and the tendency to feel excluded, this further decreases interoceptive abilities,[78] creating an amplifying feedback loop.

Difficulty in identifying and describing one's emotions, as often seen in BPD,[84-86] is phenomenologically closely related to alexithymia, a subclinical personality trait characterized by difficulty or inability to verbalize one's own emotional states[87] and related to difficulty in emotional regulation.[88] Alexithymia has also been shown to be highly prevalent in BPD[75] and has further been empirically linked with low interoceptive capabilities.[89] It is postulated that based on studies of Heartbeat evoked potentials (HEP) that those with BPD do not differ from healthy volunteers in raw visceral-afferent neurotraffic and lower-brain relaying of this information, but the deficits being found in the integration of these afferent signals into neural self-representation.[73] This overall reduced visceral and emotional awareness may mediate the relationship between adverse early life experiences and emotional regulation deficits in adulthood.[90-92]

Unique sensory and pain processing in BPD

A common and distinct behavior found in BPD is the high prevalence (69-90%[93]) of nonsuicidal self-injury (NSSI).[94] This is typically in the form of skin cutting or burning.[95-97]. The most common motive cited for this behavior are dissociation or a reduction in aversive inner tension or feelings.[96, 97] Many report an analgesic effect during self-injury.[98] This is a stark difference from PTSD, in which

hyperalgesia – increased sensitivity to pain – is prominent.[99] In fact, there seems to be a unique "pain paradox" found within BPD in which an individual may appear nearly impervious to acute pain as reported during episodes of self-mutilation, but conversely seem to be more sensitive to chronic pain than non-BPD individuals.[100]

It appears that pain stimuli of high intensity such as in cutting behavior serves as a potent modulator of stress in this population.[101] This seems to have neurobiological mechanisms, some aspects of which still seem unclear. According to Schmahl[101] "NSSI may be interpreted as an attempt to compensate for a deficient emotion regulation mechanism...the reported findings implicate that the soothing effect of pain in BPD seems to be mediated by different emotion regulation processes (attentional shift and altered appraisal of pain)" Furthermore, "it could be either due to a direct paradoxical feedback mechanism between (self-) injury and stress with stress decrease following injury though autonomic-limbic pathways, or could be due to the pain experience associated with the injury with a paradoxical feedback there (pain leads to a *decrease* in stress) in the nociceptive and limbic-behavioral networks, or both".

Acute pain seems to be associated with a complex pattern of heightened co-activation of sensory (e.g. basal ganglia), affective (e.g. amygdala), self-referential (i.e. default mode network [DMN] – precuneus, posterior cingulate), and executive inhibitory (e.g. medial and dorsolateral prefrontal cortex [PfC]) regions.[102 28] There also seems to be less integration and connectivity of the PfC with the DMN and an attenuated DMN response[103] which is associated with dissociation.[104] The insular cortex also plays an important role in the processing of painful stimuli, with impairment potentially resulting in decreased pain sensitivity or increased pain sensitivity as part of a larger network.[105] As will be explored below, recent neuroimaging studies in BPD have shown structural and functional abnormalities in a frontolimbic network including the cingulate cortex, insula, and amygdala and their connections.[106] This bears correlation with disturbed processing of emotional aspects of pain[107] while interactions between increased pain-induced response in the dorsolateral prefrontal cortex coupled with deactivations in the anterior cingulate cortex could be interpreted as an antinociceptive mechanism in BPD.[108]

Neurochemical Dysregulations Associated with BPD

Oxytocin

A dysregulation of oxytocin has been demonstrated in BPD and has been proposed to perhaps explain interpersonal difficulties and hypersensitivity.[109] Oxytocin plays an essential role in affiliative behaviors such as parental bonding and romantic partnering.[110,111] Oxytocin abnormalities in BPD clinically manifest in misreading social cues, difficulties in establishing trust, and an impacted capacity for attachment.[112]

Oxytocin levels have been shown to be negatively correlated with a childhood history of trauma,[113] which seems to be moderated by SNP rs53576 in the oxytocin receptor gene (OXTR).[114] Women with BPD have been shown to have significantly lower plasma levels of oxytocin compared to a control group;[113] while individuals with BPD showed a marked reduction in oxytocin plasma levels after social exclusion.[115] Administration of intranasal oxytocin seems to diminish hypersensitivity to and avoidant reactions to negative facial expressions[116] as well as significantly reducing stress-related dysphoria and cortisol levels in those with BPD.[117] Neuroimaging studies consistently found the amygdala responses to emotional stimuli are reduced by oxytocin administration.[118] It is of important note that while intranasal administration of oxytocin in individuals without BPD has been shown to significantly enhance trustworthiness and attractiveness toward other people,[119] individuals with BPD showed the treatment to have an opposite trust-lowering effect[120,121] which is correlated with a history of childhood trauma.[121]

Endogenous Opioids

A dysregulation of the endogenous opioid system in the form of low basal opioid levels with a compensatory supersensitivity to μ-opioid receptors in BPD has gathered increasing evidence.[114] Some primary symptoms of BPD including chronic dysphoria, lack of sense of well-being, and feeling empty inside are manifestations of low basal opioid levels.[114] The endogenous opiate system, through the μ-opioid receptors, has long been implicated in emotional regulation and stress responses.[122,123] In animal models opioid dysfunction has been associated with attachment behavior deficits and anxiety-like responses.[124, 125] A more recent study showed μ-receptor genes having a role in moderating the effects of social rejection on depression,[126] which may explain the severe reaction of BPD to interpersonal rejections.[114]

While in a neutral emotional state, individuals with BPD showed more μ-opioid binding in the prefrontal cortex, the reward center (accumbens), and the amygdala. In situations where sadness was induced they showed greater μ-opioid receptor-mediated neurotransmission than controls.[127] The investigators interpreted this greater availability as a reflection of deficient circulating endogenous opiates as a compensatory response. Naltrexone, an opioid antagonist has been shown to reduce nonsuicidal self-injury behavior in BPD, which may a result of decreasing the rewarding effects of these behaviors (sudden increase in opiates) by blocking the receptors.[128]

Brain Imaging and Functional Neuropathology

BPD has been associated with reduced top-down regulatory prefrontal cortex activity (orbitofrontal cortex, anterior cingulate cortex [ACC]), along with enhanced amygdala and insula activity.[129-135] Structural MRI studies suggest individuals with BPD have decreased volume in brain regions associated with emotion processing and regulation, which include the amygdala (left: 23%, right: 21%),[136-138] hippocampus (left: 11%, right: 16%),[136,137,139] orbitofrontal cortex,[140] and the ACC.[132,140,141]

There has been a demonstrated increase in grey matter volume in the bilateral supplementary motor area extending into the posterior cingulate cortex, primary motor cortex, right middle frontal gyrus and bilateral precuneus. Decreased grey matter was found in the bilateral middle temporal gyri, right inferior frontal gyrus extending to the right insula, left hippocampus and left superior frontal gyrus extending to left medial orbitofrontal cortex which includes frontolimbic circuits and the default mode network.[142]

Another study showed decreased fractional anisotropy (FA), a measure of white matter integrity, in the corpus callosum, corona radiata, and dorsal areas of the ACC in BPD.[143] Abnormalities in central white matter structure and long tracts in the limbic system seem present in almost all diffusion tensor imaging (DTI) studies in BPD, tending to support the fronto-limbic disconnectivity hypothesis and underscoring the possibility that abnormal maturation of white matter structures may play an important mechanistic role in BPD.[114]

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.

A reduction in hippocampal volume has been associated with stress, hypothesized to be related to

increased levels of glucocorticoids, reduced levels of brain-derived neurotrophic factor, inhibition of neurogenesis, and other factors.[137] The hippocampus contains high levels of glucocorticoid receptors which make it more vulnerable to chronic stress than most other brain areas[144]. 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. Hippocampal activity has been correlated with attachment-anxiety scores from the Experiences in Close Relationships Scale (ECR).[145] Consistent findings of impaired verbal and nonverbal recall[146] and short-term memory impairment found in BPD may be attributed to reduced hippocampal volume.

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 structures such as the hypothalamus, hippocampus, and basal prosencephalon. This will determine the behavioral, autonomic and neurohormonal function and its manifestation. LeDoux[147] 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; the amygdala essentially “overriding” the higher order actions of the prefrontal cortex. It has been put forth that in BPD, hypervigilance to fear, either conscious or unconscious, is expressed by heightened tone of relevant amygdala circuitry. This idea is supported by the positive correlations between amygdala connectivity and clinical measures such as state/trait anxiety and interpersonal sensitivity during both covert and overt fear, with interpersonal sensitivity found during covert fear.[148]

Anterior Cingulate Cortex

The anterior cingulate may serve a critical gating function in modulating conditioned fear responses and emotional regulation.[145] This includes the subjective experience of social rejection[149] and hormonal responses to stress.[150] The ACC also seems to play a role in attachment which may be particularly dependent on non-conscious implicit information processing and associated with nonlanguage-related functions lateralized to the right hemisphere.[151] The midline orbitofrontal and ACC areas are ideally situated anatomically and functionally to implement the control system of attachment and subserve fundamental “personality” defining functions.[152] An amygdala-locus coeruleus-anterior cingulate circuit may be consistent with evidence for chronic noradrenergic activation documented in BPD 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 BPD.[153] Findings of significantly higher SAIS-negative affectivity, CERQ-negative subscale, CES-D, and STAI scores alongside cognitive emotion regulation scores being negatively correlated with left ACC-CC rsFC, and depressive scores negatively correlated with left ACC–right MFG rsFC in BPD patients compared to a control group point to the potential role of the ACC regarding the heightened negative intensity, depression, and anxiety levels as well as reliance on negative emotion cognition regulation strategies in BPD.[154]

Prefrontal Cortex and Orbitofrontal 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[155]. Brain imaging studies have demonstrated reduced

volume and interconnections of the frontal lobes with other cerebral regions in individuals with different psychological disorders such as BPD[156]. Orbitofrontal cortex lesions tend to produce disinhibited or socially inappropriate behavior and emotional irregularities. Investigations have demonstrated that affected OFC function may contribute to the impulsive behavior found in BPD.[157] The dorsolateral prefrontal cortex, which has a key role in the regulation of emotions, has been demonstrated to be less active during the processing of negative emotional stimuli in BPD.[158]

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.[159] 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.[160,161]

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 BPD, individuals may feel "numb", with no access to their feelings. This may result in gustatory disconnect and associated anorexia. Symptoms which elicit greater physical sensory stimuli such as nonsuicidal 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.[161, 162]

Findings of higher insula activation have been found in response to emotional trauma-unrelated stimuli.[163,164] Analyses have confirmed childhood early life stress (ELS) events to be associated with volumetric reductions in the ACC and insula volumes. 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[165]. 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 BPD 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 which lie prominent in BPD.[166]

Cerebellum

The cerebellum plays a crucial role in motor, cognitive, and behavioral development.[167] Recent evidence in pediatric populations point to prenatal cerebellar lesions causing changes in distal regions of the brain to which the cerebellum projects, causing long-term effects on behavior, affective regulation,[168] and neuropsychiatric symptoms.[169, 170] Neuropsychiatric effects have been placed into five domains: control of attention, control of emotion, social skill set, psychosis spectrum disorders, and autism spectrum disorders.[169] The limbic cerebellum is represented by the vermis and fastigial nucleus while the cognitive cerebellum is represented by lateral hemispheres of the posterior cerebellum.[171] Impaired social interaction, aggressiveness, pervasive disturbance of behavior, and self-harming behavior are noted in cases of vermis agenesis.[172] Multiple case studies have been presented demonstrating cases in which cerebellar lesions have manifested in BPD symptomology and diagnosis.[173,174] In a study applying low frequency (1Hz) repetitive transcranial magnetic stimulation (rTMS) to the left cerebellar region of BPD patients there was demonstrated improvement in an Affective Go/No-go task testing impulsivity which increased scores to those similar to control group performance. The location was 1cm inferior and 3 cm left of the inion. From this it was hypothesized

the BPD patients may have altered cerebello-thalamo-cortical functional connections resulting in emotional dysregulation and disturbed impulse control and the rTMS seems to interfere with functional connections and with a facilitating effect on prefrontal inhibitory control.[175]

Proposed Mechanisms of Acupuncture in BPD

A number of bioregulatory mechanisms of acupuncture treatment relevant in treating patients with BPD will be put forth and explored. These include:

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

Acupuncture Effects 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 [176,177,178]

Endogenous Opioids

Acupuncture has been shown to mediate endogenous opioid pathways[179,180]. Activation of enkephalinergic neurons in several brain areas that regulate sympathetic outflow have been demonstrated, including the arcuate nucleus, rostral ventrolateral medulla, raphe nuclei, among others[181,182]. Li et al.[183] 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.[184] 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.[185] The hypothalamus is one of the largest manufacturers of beta-endorphins, the body's endogenous polyopioids which reduce pain. These opioid 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.[186] Given the evidence of dysregulation in the form of low basal opioids in individuals with BPD, acupuncture's ability to modulate this system is of significant therapeutic interest.

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.[187] 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[188,189] and ventrolateral periaqueductal grey[181,190] were activated by electroacupuncture at the P5-P6 acupoints. Glutamate only partially, but significantly, contributes to the activation of arcuate nucleus-ventrolateral periaqueductal gray reciprocal pathways during electroacupuncture stimulation of somatic afferents.[191] Electroacupuncture modulates the sympathoexcitatory reflex responses by decreasing the release of GABA in the ventrolateral periaqueductal grey,[192] which disinhibits ventrolateral periaqueductal grey cells, in turn, modulating the

activity of rostal ventrolateral medulla neurons to attenuate sympathoexcitatory reflex responses.

Nerve Growth Factor (NGF)

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[193] by a long-lasting depression of the sympathetic branch, which is associated with a peripheral downregulation of nerve growth factor in organs. Manneras et al.[194] found that electroacupuncture could effectively improve poly-cystic ovarian syndrome (PCOS)-related metabolic disorders, alter sympathetic markers[195], 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.[196] 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,[197,198] 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.[199, 200]

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 to change autonomic functions.[201] 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.[202,203] Corticotropin-releasing hormone[204] expressions in the periventricular nucleus may also suppress the sympathetic outflow in response to chronic stressors.[205]

Medulla Oblongata

Specific regions of the medulla oblongata mediate central control of autonomic functioning. Electroacupuncture could inhibit cardiovascular autonomic responses through modulating rostral ventrolateral medulla neurons[206,207] 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 rostral ventrolateral medulla.[208] Activation of the nucleus raphe pallidus attenuates sympathoexcitatory cardiovascular reflexes through a mechanism involving serotonergic neurons and 5-HT1A receptors in the rostral 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 release of acetylcholine.[208] Some nucleus ambiguus neurons activated by electroacupuncture are preganglionic vagal neurons.[209] 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.[210] 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.[211]

Dorsomedial Prefrontal Cortex (DMPFC)
The prefrontal cortex is vital for mediating behavioral and somatic responses to stress in the autonomic centers via projections.[212] A near-infrared spectroscopy study found that the right prefrontal cortex activity predominantly modulated sympathetic effects during a mental stress task.[213] It is speculated that acupuncture may decrease sympathetic activity and increase parasympathetic activity through its effects on dorsomedial prefrontal cortex activity.[214]

Influence of Acupuncture on Cortical Regions
A number of points have been demonstrated by fMRI studies to have a correlation to brain activity relevant to the current topic.[215]

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.[216]

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.[217]

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. This has been demonstrated repeatedly, especially a well-defined deactivation effect in the left amygdala.[218] 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.[219]

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.[220]

Acupoint PC-6

Neuroimaging studies of PC-6 presented extensive signal attenuation in the cerebrocerebellar and subcortical areas. Compared to other points tested (PC-7, GB-37), PC-6 selectively evoked neural responses in the insula, hypothalamus, and flocculonodular lobe of the cerebellum.[221]

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.[222]

Regional Acupuncture Effects

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 an additive effect of acupuncture to antidepressant treatment suggested to be achieved through the limbic system, especially the amygdala and the anterior cingulate cortex.[223]

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 exhibit relative specificity.[224]

Hippocampus
In a meta-analysis of fMRI studies GB-34 and GB-39 had a demonstrated activating effect on the hippocampus.[223] 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.[225] 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.[226] 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.[220]

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.[227]

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.[228, 229]

Discussion
Based on presented studies, an evidence-based neurobiological treatment approach of BPD with acupuncture may be developed. Protocols can be established based on evidence-based fMRI studies of cortical region activations and deactivations by acupuncture point stimulation correlating with findings and understandings of neurological changes tending to occur in BPD. This treatment approach would thus focus on the cerebellum, limbic structures including the insula, amygdala and hippocampus, the anterior cingulate cortex, and medial prefrontal cortex. Based on this criteria points that may be considered are BL-10, GB-20, 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/GV-20. 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
Electroacupuncture (2-10Hz): BL-10(left) →GV-20
Total Points Used: 13

Auricular protocols such as the 5NP NADA protocol may also be considered in their bio-regulatory effect of the autonomic nervous system and upregulation of endogenous opioids while being easily accessible by 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.[212]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. 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 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 BPD 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 a neurobiological mechanism of acupuncture can be established in a BPD model and that it is possible to apply these findings clinically. This may allow the practitioner to be able to treat their patient with evidence-based treatment approaches. This is not meant or intended to supersede traditional acupuncture treatment approaches, diagnostics, or pattern differentiation, but to hopefully 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. Huang Y, Kotov R, de Girolamo G, Preti A, Angermeyer M, Benjet C, Demyttenaere K, de Graaf R, Gureje O, Karam AN, Lee S, Lépine JP, Matschinger H, Posada-Villa J, Suliman S, Vilagut G, Kessler RC. DSM-IV personality disorders in the WHO World Mental Health Surveys. Br J Psychiatry 2009;195:46–53.
2. Jackson HJ, Burgess PM. Personality disorders in the community: a report from the Australian National Survey of Mental Health and Wellbeing. Soc Psychiatry Psychiatr Epidemiol 2000;35:531–8.
3. Lenzenweger MF, Lane MC, Loranger AW, Kessler RC. DSM-IV personality disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007;62:553–64.
4. ten Have M, Verheul R, Kaasenbrood A, van Dorsselaer S, Tuithof M, Kleinjan M, de Graaf R. Prevalence rates of borderline personality disorder symptoms: a study based on the Netherlands mental Health Survey and Incidence Study-2. BMC Psychiatry 2016;16:249.
5. Tomko RL, Trull TJ, Wood PK, Sher KJ. Characteristics of borderline personality disorder in a community sample: comorbidity, treatment utilization, and general functioning. J Pers Disord 2014;28:734–50.
6. Black DW, Blum N, Letuchy E, Carney Doebbeling C, Forman-Hoffman VL, Doebbeling BN. Borderline personality disorder and traits in veterans: psychiatric comorbidity, healthcare utilization, and quality of life along a continuum of severity. CNS Spectr 2006;11:680–9.
7. Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G, Weinberg I, Gunderson JG. The 10-year course of physically self-destructive acts reported by borderline patients and axis II comparison subjects. Acta Psychiatr Scand 2008;117:177–84.
8. Bender DS, Skodol AE, Pagano ME, Dyck IR, Grilo CM, Shea MT, Sanislow CA, Zanarini MC, Yen S, McGlashan TH, Gunderson JG. Prospective assessment of treatment use by patients with personality disorders. Psychiatr Serv 2006;57:254–7.
9. Keuroghlian AS, Gunderson JG, Pagano ME, Markowitz JC, Ansell EB, Shea MT, Morey LC, Sanislow C, Grilo CM, Stout RL, Zanarini MC, McGlashan TH, Skodol AE. Interactions of borderline personality disorder and anxiety disorders over 10 years. J Clin Psychiatry 2015;76:1529–34.
10. Sansone RA, Sansone LA. Borderline Personality disorder in the medical setting: suggestive behaviors, syndromes, and Diagnoses. Innov Clin Neurosci 2015;12:39–44.
11. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5. Washington, DC: American Psychiatric Association, American Psychiatric Press; 2013.
12. Hyler SE. Personality Questionnaire-4+. New York: State Psychiatric Institute; 1994.
13. Hyler SE, SkodolAE, Kellman HD, Oldham JM, Rosnick L. Validity of the Personality Diagnostic Questionnaire—Revised: comparison with two structured interviews. Am J Psychiatry 1990;147:1043–8.
14. Schotte CK, de Doncker D, Vankerckhoven C, Vertommen H, Cosyns P. Selfreport assessment of the DSM-IV personality disorders. Measurement trait and distress characteristics: the ADP-IV. Psychol Med 1998;28:1179–88.
15. Bohus M, Limberger MF, Frank U, Chapman AL, Kuhler T, Stieglitz RD. Psychometric properties of the Borderline Symptom List (BSL). Psychopathology 2007;40:126–32.
16. Amad, A, Ramoz, N, Thomas, P, Gorwood, P. The age-dependent plasticity highlights the conceptual interface between borderline personality disorder and PTSD. Eur Arch Psychiatry Clin Neurosci. 2015, Oct 12.
17. Zanna AS, Binder EB (2014) Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. Genes Brain Behav 13:25-37. doi:10.1111/gbb.12104
18. Amad A, Ramoz, N Thomas P et al. Geneteics of borderline personality disorder: systematic review and proposal of an integrative model. Neurosci Biobehav Rev 2014. 40C:6-19. Doi: 10.106/j.neubiorev.2014.01.003.
19. Gunderson JG, Sabo AN.The phenomenological and conceptual interface between borderline personality disorder and PTSD. Am J Psychiatry 1993. 150:19-27
20. Lewis KL, Grenyer, BFS. Borderline personality disorder or complex posttraumatic stress disorder? An update on the controversy. Harv Rev Psychiatry 2009. 17:322-328. doi: 10.3109/10673220903271848
21. Krause-Utz A, Winter D, Niedtfeld I, Schmahl C (2014) The latest neuroimaging findings in borderline personality disorder. Curr Psychiatry Rep 16:438. doi:10.1007/s11920-014-0438-z
22. Patel R, Spreng RN, Shin LM, Girard TA. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-anal-ysis of functional neuroimaging studies. Neurosci Biobehav Rev 2012. 36:2130–2142. doi:10.1016/j.neubiorev.2012.06.003
23. de Kloet CS, Vermetten E, Geuze E et al . Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. J Psychiatr Res 2006.40:550–567. doi:10.1016/j.jpsychires.2005.08.002
24. Wingenfeld K, Spitzer C, Rullkötter N, Löwe B. Border-line personality disorder: hypothalamus pituitary adrenal axis and findings from neuroimaging studies. Psychoneuroendocri-nology 2010. 35:154–170.

doi:10.1016/j.psyneuen.2009.09.014
25. Martin-Blanco A, Ferrer M, Soler J et al. The role of hypothalamus-pituitary-adrenal genes and childhood trauma in borderline personality disorder. Eur Arch Psychiatry Clin Neuro-sci. 2015. Doi: 10.1007/s00406-015-0612-2.
26. Cloitre, M, Garvert, D, Weiss, B, Carlson, E, Bryant, R. Distinguishing PTSD, Complex PTSD, and borderline personality disorder: a latent class analysis. Eurpean Journal of Psychotraumology. 2014, 5: 25097. http://dx.doi.org/10.3402/ejpt.v5.25097
27.Cloiter M, Garvert D.W, Brewin C. R, Bryant R. A, Maercker A. Evidence for proposed ICD-11 PTSD and Complex PTSD: a lent profile analysis. European Journal od Psychotraumatology. 2013; 4 20706, doi: http://dx.doi.org/10.3402/ejpt.v4i0.20706
28. Ford, J, Courtois, C. Complex PTSD, affect dysregulation, and borderline personality disorder. Borderline Personality Disorder and Emotional Dysregulation. 2014, 1:9. http://www.bpded.com/content/1/1/9.
29. Kolb B, Gibb R. Searching for the principles of brain plasticity and behavior. Cortex 2014. 58:251–260. doi:10.1016/j.cortex.2013.11.012 7.
30. Kolb, B, Gibb, R. Brain plasticity and recovery from early cortical injury. Dev Psychobiol 2007. Mar; 49(2):107-18
31. Shalev, A.Y., Videlock, E.J., Peleg, T, Segman, R, Pitman, R.K., Yehuda, R. Stress hormones and post-traumatic stress disorder in civilization trauma victims: a longitudinal study, Part I: HPA axis responses. Int J Neuropsychopharmacol. 11, 365-372. http://doi.org/10.1017/S1461145707008127
32. Amad, A, Radua, J, Vaiva, G, Williams, SCR, Fovet, T. Similarities between Borderline Personality Disorder and post traumatic stress disorder: evidence from resting-state meta-analysis. 2019. May doi: 10.1101/633248
33. Ball, J., Links, P. Borderline personality disorder and childhood trauma: Evidence for a causal relationship. Curr. Psychiatry Rep. 2009. 11, 63–68. https://doi.org/10.1007/s11920-009-0010-4
34. Zanarini, M.C., Yong, L., Frankenburg, F.R., Hennen, J., Reich, D.B., Marino, M.F., Vujanovic, A.A., Severity of reported childhood sexual abuse and its relationship to severity of borderline psychopathology and psychosocial impairment among borderline inpatients. J. Nerv. Ment. Dis. 2002. 190, 381–387.
35. McLean, L, Gallop, R, Implications of childhood sexual abuse for adult borderline personality disorder and complex posttraumatic stress disorder. Am J Psychiatry 2003. 160:369-371
36. Schmahl CG, Elzinga BM, Ebner UW, Simms T, Sanislow C, Vermetten E, BremnerJD:Psychophysiological reactivity to traumatic and abandonment scripts inborderline personality and posttraumatic stress disorders: a preliminaryreport.Psychiatry Res 2004,126(1):33–42. doi:10.1016/j.psychres.2004.01.005
37. Lis S, Bohus M:Social interaction in borderline personality disorder.[Review].Curr Psychiatr Rep 2013,15(2):338. doi:10.1007/s11920-012-0338-z
38. Schore AN:Attachment and the regulation of the right brain.Am J Bioeth 2000,2(1):23–47. Doi:10.1080/146167300361309
39. Lyons-Ruth K:Contributions of the mother-infant relationship to dissociative,borderline, and conduct symptoms in young adulthood.Infant Ment Health J 2008,29(3):203–218. doi:10.1002/imhj.20173.
40. Zanarini MC, Frankenburg FR, Reich DB, Marino MF, Lewis RE, Williams AA,Khera GS:Biparental failure in the childhood experiences of borderlinepatients.J Personal Disord 2000,14(3):264–273.
41. Agrawal HR, Gunderson J, Holmes BM, Lyons-Ruth K:Attachment studieswith borderline patients: a review. [Review].Harv Rev Psychiatry 2004,12(2):94–104. doi:10.1080/10673220490447218.
42.Zanarini MC, Frankenburg FR:The essential nature of borderlinepsychopathology.J Personal Disord 2007,21(5):518–535. doi:10.1521/pedi.2007.21.5.518.89.
43. Gunderson JG, Lyons-Ruth K:BPD's interpersonal hypersensitivity phenotype: a gene-environment-developmental model.J Pers Disord 2008,22(1):22–41. doi:10.1521/pedi.2008.22.1.22.90.
44. Lyons-Ruth K:Contributions of the mother-infant relationship to dissociative,borderline, and conduct symptoms in young adulthood.Infant Ment Health J 2008,29(3):203–218. doi:10.1002/imhj.20173.
45. 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.
46. Wingate, D. Acupuncture in the Treatment of Post-Traumatic Stress Disorder: A Neurobiological Approach. 2019.
47. Drews, E, Fertuck, E.A., Koenig, J, Kaess, M, Arntz, A. Hypothalamic-pituitary-adrenal axis functioning in borderline personality disorder: A meta-analysis. Neurosci. Biobehav. Rev. 2019. 96, 316-334. http://doi.org/10.1016/j.neubiorev.2018.11.008
48. Wingenfeld, K, Spitzer, C, Rullkotter, N, Lowe, B. Borderline personality disorder: Hypothalamus pituitary adrenal axis and findings from neuroimaging studies. 2010. Psychoneuroendocrinology 35, 154-170. http://doi.org/10.1016/j.psyneun.2009.09.014
49. Kuhlman, A, Vargas, I, Geiss, E, Lopez-Duran N. Age of trauma onset and HPA axis dysregulation among trauma-exposed youth. Journal of Traumatic Stress. 2015 Dec., 28, 572-579.doi: 10.1002/jts.22054.
50. Doering, S. Borderline Personality Disorder in patients with medical illness: a review of assessment, prevalence, and

treatment options. Psychosomatic Medicine. 2019 Sept. 81, 584-594. doi: 10.1097/PSY.0000000000000724
51. ten Have M, Verheul R, Kaasenbrood A, van Dorsselaer S, Tuithof M, Kleinjan M, de Graaf R. Prevalence rates of borderline personality disorder symptoms: a study based on the Netherlands mental Health Survey and Incidence Study-2. BMC Psychiatry 2016;16:249.
52. Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, Smith SM, Dawson DA, Pulay AJ, Pickering RP, Ruan WJ. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2008;69:533–45.
53. Silverman MH, Frankenburg FR, Reich DB, Fitzmaurice G, Zanarini MC. The course of anxiety disorders other than PTSD in patients with borderline personality disorder and axis II comparison subjects: a 10-year follow-up study. J Pers Disord 2012.26:804–14.
54. McGlashan TH, Grilo CM, Skodol AE, Gunderson JG, Shea MT, Morey LC, Zanarini MC, Stout RL. The Collaborative Longitudinal Personality Disorders Study: baseline axis I/II and II/II diagnostic co-occurrence. Acta Psychiatr Scand 2000.102:256–64.
55. Rosenvinge JH, Martinussen M, Ostensen E. The comorbidity of eating disorders and personality disorders: a meta-analytic review of studies published between 1983 and 1998. Eat Weight Disord 2000.5:52–61.
56. Zanarini MC, Reichman CA, Frankenburg FR, Reich DB, Fitzmaurice G. The course of eating disorders in patients with borderline personality disorder: a 10-year follow-up study. Int J Eat Disord 2010.43:226–32
57. Bayes A,Parker G. Cognitive and behavioral differentiation of those with borderline personality disorder and bipolar disorder. The Journal of Nervous and Mental Disease. 2019 Aug. .V207(8). 620-625. doi: 10.1097/NMD.0000000000001024.
58. Frankenburg FR, Zanarini MC. Personality disorders and medical comorbidity. Curr Opin Psychiatry 2006;19:428–31
59. Sansone RA, Bohinc RJ, Wiederman MW. Borderline personality symptomatology and compliance with general health care among internal medicine outpatients. Int J Psychiatry Clin Pract 2015.19:132–6.
60. Sansone RA, Wiederman MW, Sansone LA. Medically self-harming behavior and its relationship to borderline personality symptoms and somatic preoccupation among internal medicine patients. J Nerv Ment Dis 2000;188:45–7.
61. Sansone RA, Sansone LA. Borderline Personality disorder in the medical setting: suggestive behaviors, syndromes, and Diagnoses. Innov Clin Neurosci 2015.12:39–44
62. El-Gabalawy R, Katz LY, Sareen J. Comorbidity and associated severity of borderline personality disorder and physical health conditions in a nationally representative sample. Psychosom Med 2010.72:641–7.
63.Craig, A. D. How do you feel — now? the anterior insula and human awareness. Nat. Rev. Neurosci. 2009. 10, 59–70. doi: 10.1038/nrn2555
64. Schulz A, Vögele C. Interoception and stress. Front Psychol.2015;6:993.
65. Arnold, A, Winkielman, P, Dobkins, K. Interoception and social connection. Frontiers in Psychology. 2019 Nov 26. doi: 10.3389/fpsyg.2019.02589
66.Janig W. Neurobiology of visceral afferent neurons: neuroanatomy,functions, organ regulations and sensations. Biol Psychol.1996. 42(1–2):29–
67. Critchley HD,Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. Nat Neurosci. 2004. 7(2):189–95. https://doi.org/10.1038/nn1176.
68. Garfinkel SN, Seth AK, Barrett AB, Suzuki K, Critchley HD.Knowing your own heart: distinguishing interoceptive accuracyfrom interoceptive awareness. Biol Psychol. 2015. 104:65–74.
69. Craig, A. D. How Do You Feel? An Interoceptive Moment With Your Neurobiological Self. Princeton, NJ: Princeton University Press. 2015.
70. Forkmann T, Scherer A, Meessen J, Michal M, Schächinger H,Vögele C, et al. Making sense of what you sense: disentanglinginteroceptive awareness, sensibility and accuracy. Int JPsychophysiol. 2016.109:71–80.
71. Brewer R, Cook R, Bird G. Alexithymia: a general deficit of interoception. R Soc Open Sci. 2016;3(10):150664. https://doi.org/10.1098/rsos.150664.
72. Murphy J, Brewer R, Catmur C, Bird G. Interoception and psychopathology: a developmental neuroscience perspective. Dev Cogn Neurosci. 2017. 23:45–56. https://doi.org/10.1016/j.dcn.2016.12.006.
73. Müller LE, Schulz A, Andermann M, Gäbel A, Gescher DM, Spohn A, et al. Cortical representation of afferent bodily signals in borderline personality disorder: neural correlates and relationship to emotional dysregulation. JAMA psychiatry. 2015. 72(11): 1077–86.
74. Shah P, Hall R, Catmur C, Bird G. Alexithymia, not autism, is associated with impaired interoception. Cortex. 2016. 81:215–20.
75. New AS, aan het Rot M, Ripoll LH, Perez-Rodriguez MM, Lazarus S, Zipursky E, et al. Empathy and alexithymia in borderline personality disorder: clinical and laboratory measures. J Personal Disord. 2012. 26(5):660–75. https://doi.org/10.1521/pedi.2012.26.5.660.
76. Linehan M. Cognitive-behavioral treatment of borderline personality disorder. Guilford press; 1993.
77. Crowell SE, Beauchaine TP, Linehan MM. A biosocial developmental model of borderline personality: elaborating and

extending linehan's theory. Psychol Bull. 2009. 135(3):495.
78. Loffer, A, Foell, J, Bekrater-Bodmann, R. Interoception and its interaction with self, other, and emotion processing: implications for understanding the psychosocial deficits in borderline personality disorder. Current Psychiatry Reports. 2018. 20: 28. http://doi.org/10.1007/s11920-018-0890-2.
79. Gunderson JG, Fruzzetti A, Unruh B, Choi-Kain L. Competingtheories of borderline personality disorder. J Personal Disord. 2018. 32(2):148–67
80. Back, S, Bertsch, K. Interoceptive processing in borderline personality pathology: a review on neurophysiological mechanisms. Current Behavioral Neuroscience Reports. 2020. 7:232-238. http://doi.org/10.1007/s40473-020-00217-2.
81. Linehan MM. Diagnosis and treatment of mental disorders.Cognitive-behavioral treatment of borderline personality disorder.New York: Guilford Press; 1993.
82. Schaan VK, Schulz A, Bernstein M, Schächinger H, Vögele C.Effects of rejection intensity and rejection sensitivity on social ap-proach behavior in women. PLoS One. 2020. 15(1):e0227799.
83. Reinhardt, K, Zerubavel, N, Young, A, Gallo, M, Ramakrishna, N, Henry, A, Zucker, N. A multi-method assessment of interoception among sexual trauma survivors. Physiology and Behavior 226. 2020. 113108. http://doi.org/10.1016/j.physbeh.2020.113108
84. Coifman KG, Berenson KR, Rafaeli E, Downey G. From negative to positive and back again: polarized affective and relational experience in borderline personality disorder. J Abnorm Psychol. 2012. 121(3):668.
85. Leible TL, Snell WE Jr. Borderline personality disorder and multiple aspects of emotional intelligence. Pers Individ Dif. 2004. 37(2):393–404.
86. Suvak MK, Litz BT, Sloan DM, Zanarini MC, Barrett LF, Hofmann SG. Emotional granularity and borderline personality disorder. J Abnorm Psychol. 2011. 120(2):414.
87. Sifneos PE. The prevalence of 'alexithymic' characteristics in psychosomatic patients. Psychother Psychosom. 1973. 22(2):255–62.
88. Silva AN, Vasco AB, Watson JC. Alexithymia and emotional processing: a mediation model. J Clin Psychol. 2017. 73(9): 1196–205.
89. Herbert BM, Herbert C, Pollatos O. On the relationship between interoceptive awareness and alexithymia: is interoceptive awareness related to emotional awareness? J Pers. 2011. 79(5):1149–75. https://doi.org/10.1111/j.1467-6494.2011.00717.x.
90. Aust S, Härtwig EA, Heuser I, Bajbouj M. The role of early emotional neglect in alexithymia. Psychol Trauma. 2013. 5(3):225.
91. Swannell S, Martin G, Page A, Hasking P, Hazell P, Taylor A, et al. Child maltreatment, subsequent non-suicidal self-injury and the mediating roles of dissociation, alexithymia and self-blame. Child Abuse Negl. 2012. 36(7):572–84.
92. Paivio SC, McCulloch CR. Alexithymia as a mediator between childhood trauma and self-injurious behaviors. Child Abuse Negl. 2004. 28(3):339–54. https://doi.org/10.1016/j.chiabu.2003.11.018.
93. Zanarini MC, Frankenburg FR, Reich DB, Fitzmau-rice G, Weinberg I, Gunderson JG: The 10-year course of physically self-destructive acts reported by borderline patients and axis II comparison subjects. Acta Psychiatr Scand 2008. 117: 177–184.
94. Welch SS, Linehan MM, Sylvers P, Chittams J, Rizvi SL: Emotional responses to self-injury imagery among adults with borderline personality disorder. J Consult Clin Psychol 2008. 76: 45–51.
95. Klonsky ED: The functions of deliberate self-injury: a review of the evidence. Clin Psychol Rev 2007. 27: 226–239.
96. Chapman AL, Gratz KL, Brown MZ: Solving the puzzle of deliberate self-harm: the experiential avoidance model. Behav Res Ther 2006. 44: 371–394.
97. Kleindienst N, Bohus M, Ludäscher P, Limberger MF, Kuenkele K, Ebner-Priemer UW, et al: Motives for nonsuicidal self-injury among women with bor-derline personality disorder. J Nerv Ment Dis 2008; 196: 230–236.
98. Shearer SL: Phenomenology of self-injury among in-patient women with borderline personality disorder. J Nerv Ment Dis 1994. 182: 524–526.
99. Porter KE, Pope EB, Mayer R, Rauch SA: PTSD and pain: exploring the impact of posttraumatic cognitions in veterans seeking treatment for PTSD. Pain Med 2013. 14(11):1797–1805. doi:10.1111/pme.12260
100. Sansone RA, Sansone LA. Borderline personality and the pain paradox. *Psychiatry (Edgmont)*. 2007;4(4):40-46.
101. Schmahl, C, Baumgartner, U. Pain in borderline personality disorder. Pain In Psychiatric Disorders. Mod Trends Pharmacopsychiatry. Basal, Karger, 2015. vol 30, pp 166-175. doi: 10.1159/000435940
102. Niedtfeld I, Kirsch P, Schulze L, Herpertz SC, Bohus M, Schmahl C: Functional connectivity of pain-mediated affect regulation in Borderline Personality Disorder. PLoS ONE 2012. 7(3):e33293. doi:10.1371/journal. pone.0033293.
103. Kluetsch RC, Schmahl C, Niedtfeld I, Densmore M, Calhoun VD, Daniels J, Lanius RA: Alterations in default mode network connectivity during pain processing in borderline personality disorder. Arch Gen Psychiatry 2012. 69(10):993–1002. doi:10.1001/archgenpsychiatry.2012.476.
104.Ludascher P, Valerius G, Stiglmayr C, Mauchnik J, Lanius RA, Bohus M, Schmahl C: Pain sensitivity and neural processing during dissociative states in patients with borderline personality disorder with and without comorbid

posttraumatic stress disorder: a pilot study. J Psychiatry Neurosci 2010. 35(3):177–184
105. Starr CJ, Sawaki L, Wittenberg GF, Burdette JH, Oshiro Y, Quevedo AS, et al: Roles of the insular cortex in the modulation of pain: insights from brain lesions. J Neurosci 2009. 29:2684–2694.
106. Shi CJ, Cassell M: Cortical, thalamic, and amygdaloid connections of the anterior and posterior insular cortices. J Comp Neurol 1998. 399:440–468.
107. Krause-Utz A, Winter D, Niedtfeld I, Schmahl C: The latest neuroimaging findings in borderline personality disorder. Curr Psychiatry Rep 2014. 16:1–13.
108. Schmahl C, Bohus M, Esposito F, Treede RD, Di Salle F, Greffrath W, et al: Neural correlates of antinociception in borderline personality disorder. Arch Gen Psychiatry 2006. 63:659–667.
109. Herpertz SC, Bertsch K. A new perspective on the pathophysiology of borderline personality disorder: a model of the role of oxytocin. Am J Psychiatry. 2015. 172(9):840–51.
110.Francis DD, Champagne FC, Meaney MJ. Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. J Neuroendocrinol 2000. 12(12):1145–8.
111. Grewen KM, Girdler SS, Amico J, et al. Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. Psychosom Med 2005. 67(4):531–8.
112. Stanley B, Siever LJ. The interpersonal dimension of borderline personality disorder: toward a neuropeptide model. Am J Psychiatry 2010. 167(1):24–39.
113. Bertsch K, Schmidinger I, Neumann ID, et al. Reduced plasma oxytocin levels in female patients with borderline personality disorder. Horm Behav 2013. 63(3): 424–9.
114. Perez-Rodriguez, M, Bulbena-Cabre, A, Nia, AB, Zipursky, G, Goodman, M, New, A. The neurobiology of borderline personality Disorder. Psychiatr Clin N Am 41. 2018. 41: 633-650. http://doi.org/10.1016/j.psc.2018.07.012
115. Jobst A, Sabass L, Palagyi A, et al. Effects of social exclusion on emotions and oxytocin and cortisol levels in patients with chronic depression. J Psychiatr Res 2015. 60:170–7.
116. Brune M, Ebert A, Kolb M, et al. Oxytocin influences avoidant reactions to social threat in adults with borderline personality disorder. Hum Psychopharmacol 2013. 28(6):552–61.
117. Simeon D, Bartz J, Hamilton H, et al. Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study. Psychoneuroendocrinology 2011. 36(9):1418–21.
118. Domes G, Heinrichs M, Glascher J, et al. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol Psychiatry 2007. 62(10):1187–90.
119. Theodoridou A, Rowe AC, Penton-Voak IS, et al. Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm Behav 2009. 56(1):128–32.
120. Bartz J, Simeon D, Hamilton H, et al. Oxytocin can hinder trust and cooperation in borderline personality disorder. Soc Cogn Affect Neurosci 2011. 6(5):556–63.
121. Ebert A, Kolb M, Heller J, et al. Modulation of interpersonal trust in borderline personality disorder by intranasal oxytocin and childhood trauma. Soc Neurosci 2013. 8(4):305–13.
122. Kennedy SE, Koeppe RA, Young EA, et al. Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. Arch Gen Psychiatry 2006. 63(11):1199–208.
123. Zubieta JK, Ketter TA, Bueller JA, et al. Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. Arch Gen Psychiatry 2003. 60(11):1145–53.
124. Moles A, Kieffer BL, D'Amato FR. Deficit in attachment behavior in mice lackingthe mu-opioid receptor gene. Science 2004. 304(5679):1983–6.
125. Panksepp J, Herman BH, Vilberg T, et al. Endogenous opioids and social behavior. Neurosci Biobehav Rev 1980. 4(4):473–87.
126. 104. Slavich GM, Tartter MA, Brennan PA, et al. Endogenous opioid system influences depressive reactions to socially painful targeted rejection life events. Psychoneuroendocrinology 2014. 49:141–9.
127. Prossin AR, Love TM, Koeppe RA, et al. Dysregulation of regional endogenous opioid function in borderline personality disorder. Am J Psychiatry 2010. 167(8): 925–33.
128. Sonne S, Rubey R, Brady K, et al. Naltrexone treatment of self-injurious thoughts and behaviors. J Nerv Ment Dis 1996. 184(3):192–5.
129. Brendel GR, Stern E, Silbersweig DA. Defining the neurocircuitry of borderline personality disorder: functional neuroimaging approaches. Dev Psychopathol 2005. 17(4):1197–206.
130. Dell'Osso B, Berlin HA, Serati M, et al. Neuropsychobiological aspects, comorbidity patterns and dimensional models in borderline personality disorder. Neuropsychobiology 2010. 61(4):169–79.
131. Minzenberg MJ, Fan J, New AS, et al. Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. Psychiatry Res 2007. 155(3):231–43.
132. Minzenberg MJ, Fan J, New AS, et al. Frontolimbic structural changes in borderline personality disorder. J Psychiatr Res 2008. 42(9):727–33.
133. Ruocco AC, Amirthavasagam S, Choi-Kain LW, et al. Neural correlates of negative emotionality in borderline

personality disorder: an activation-likelihood estimation meta-analysis. Biol Psychiatry 2013. 73(2):153–60.
134. Schmahl C, Bremner JD. Neuroimaging in borderline personality disorder. J Psychiatr Res 2006. 40(5):419–27.
135. Wingenfeld K, Rullkoetter N, Mensebach C, et al. Neural correlates of the individual emotional Stroop in borderline personality disorder. Psychoneuroendocrinology 2009;34(4):571–86.
136. Nunes PM, Wenzel A, Borges KT, et al. Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. J Pers Disord 2009;23(4):333–45.
137. Schmahl, C, Vermetten, E, Elzinga, B, Bremner, J. Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. Psychiatry research: Neuroimaging. 2003. 122: 193-198
138. Tebartz van Elst L, Ludaescher P, Thiel T, et al. Evidence of disturbed amygdalar energy metabolism in patients with borderline personality disorder. Neurosci Lett 2007;417(1):36–41.
139. Brambilla P, Soloff PH, Sala M, et al. Anatomical MRI study of borderline personality disorder patients. Psychiatry Res 2004;131(2):125–33.
140. Tebartz van Elst L, Hesslinger B, Thiel T, et al. Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. Biol Psychiatry 2003;54(2):163–71.
141. Hazlett EA, New AS, Newmark R, et al. Reduced anterior and posterior cingulate gray matter in borderline personality disorder. Biol Psychiatry 2005;58(8): 614–23.
142. Yang X, Hu L, Zeng J, et al. Default mode network and frontolimbic gray matter abnormalities in patients with borderline personality disorder: a voxel-based meta-analysis. Sci Rep 2016;6:34247.
143. Gan J, Yi J, Zhong M, et al. Abnormal white matter structural connectivity in treatment-naive young adults with borderline personality disorder. Acta Psychiatr Scand 2016;134(6):494–503.
144. Joels 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.
145. Ochsner, K. N., & Gross, J. J. (2005). The cognitivecontrol of emotion.Trends in Cognitive Sciences,9,242–249.
146.Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The med-ial temporal lobe.Annual Review of Neuroscience,27,279–306.
147. 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
148. Cullen KR, Vizueta N, Thomas KM, et al. Amygdala functional connectivity in young women with borderline personality disorder. *Brain Connect*. 2011;1(1):61-71. doi:10.1089/brain.2010.0001
149. Eisenberger, N. I., Lieberman, M. D., Williams, K. D. Does rejection hurt? An FMRI study of socialexclusion.Science 2003. 302, 290–292.
150. Diorio, D., Viau, V., & Meaney, M. J. The roleof the medial prefrontal cortex (cingulate gyrus) inthe regulation of hypothalamic–pituitary–adrenal re-sponses to stress.Journal of Neuroscience 1993. 13,3839–3847.
151. Schore, A. N. Effects of a secure attachment rela-tionship on right brain development, affect regulationand infant mental health.Infant Mental Health Journal 2001. 22, 7–66.
152. Cavada, C., & Schultz, W. The mysterious OFC.Cerebral Cortex 2000. 10, 205.
153. 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
154. Lei X, Zhong M, Zhang B, et al. Structural and Functional Connectivity of the Anterior Cingulate Cortex in Patients With Borderline Personality Disorder. *Front Neurosci*. 2019;13:971. Published 2019 Sep 13. doi:10.3389/fnins.2019.00971
155. 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
156. 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
157. Berlin HA, Rolls ET, Iversen SD. Borderline personality disorder, impulsivity, and the orbitofrontal cortex. Am J Psychiatry. 2005 Dec;162(12):2360-73. doi: 10.1176/appi.ajp.162.12.2360. PMID: 16330602.
158. Schulze, L, Schmahl, C, Niedtfeld, I. Neural Correlates of Disturbed Emotion Processing in Borderline Personality Disorder: A Multimodal Meta-Analysis. *Biological Psychiatry*, 2016 Jan 15. V79:2
159. 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
160. 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
161. Barrett LF, Simmons WK. Interoceptive predictions in the brain. *Nat Rev Neurosci*. 2015;16(7):419–429. doi:10.1038/nrn3950
162. 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
163. 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
164. 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
165. 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
166. 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
167. Limperopoulos C, Bassan H, Gauvreau K, Robertson RL Jr, Sullivan NR, Benson CB, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long term cognitive, learning, and behavioral disability in survivors? Pediatrics. 2007;120:584–93
168. Stoodley CJ, Limperopoulos C. Structure-function relationships in the developing cerebellum: evidence from early-life cerebellar injury and neurodevelopmental disorders. Semin Fetal Neonatal Med. 2016;21:356–64.
169.Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum—insights from the clinic. Cerebellum. 2007;6: 254–67.
170. 7. Pesic D, Peljto A, Lukic B, Milovanovic M, Svetozarevic S, Lecic TD. Cerebellar cognitive affective syndrome presented as severe borderline personality disorder. Case report in medicine. 2014;1–4.
171. Stoodley CJ, Schmahmann JD. "Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing," Cortex 2010. 46(7) 831–844.
172. Tavano, A, Grasso, R, Gagliardi, C et al., "Disorders of cognitive and affective development in cerebellar malformations," Brain 2007. 130(10) 2646–2660.
173. Pesic, D, Peljto, A, Lukic, B, Milovanovic, M, Svetozarevic, S, Tosevski, D. Cerebellar cognitive affective syndrome presented as severe borderline personality disorder. Case Rep Med. 2014. 2014:894263. doi: 10.1155/2014/894263.
174. Lupo, M., Olivito, G., Siciliano, L., et al. Development of a psychiatric disorder linked to cerebellar lesions. Cerebellum, 2018. 17(4), 438–46. doi: 10.1007/s12311-018-0926-5.
175. De Vidovich GZ, Muffatti R, Monaco J, et al. Repetitive TMS on Left Cerebellum Affects Impulsivity in Borderline Personality Disorder: A Pilot Study. *Front Hum Neurosci*. 2016;10:582. Published 2016 Dec 5. doi:10.3389/fnhum.2016.00582
176. 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
177. Li P, Longhurst JC. Neural mechanism of electroacupuncture's hypotensive effects. Autonomic *Neuroscience.* 2010;157(1-2):24–30.
178. Zhou W, Longhurst JC. Neuroendocrine mechanisms of acupuncture in the treatment of hypertension. *Evidence-Based Complementary and Alternative Medicine*. 2012;2012:9 pages.878673
179. 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.
180. Ouyang H, Xing J, Chen J. Electroacupuncture restores impaired gastric accommodation in vagotomized dogs. *Digestive Diseases and Sciences.* 2004;49(9):1418–1424.
181. 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.
182. 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.
183. 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.
184. 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.
185. 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.
186. Wingate, Douglas S. *Healing Brain Injury with Chinese Medical Approaches: Integrative Approaches for Practitioners*. Singing Dragon, 2018.
187. Tome 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.
188. 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.

189. Seal RP, Wang X, Guan Y, et al. Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. *Nature.* 2009;462(7273):651–655.
190. 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.
191. 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
192. Tjen-A-Looi SC, Li P, Longhurst JC. Role of medullary GABA, opioids, and nociception in prolonged inhibition of cardiovascular sympathoexcitatory reflexes during electroacupuncture in cats. *The American Journal of Physiology.* 2007;293(6):H3627–H3635.
193. Manni L, Albanesi M, Guaragna M, Paparo SB, Aloe L. Neurotrophins and acupuncture. *Autonomic Neuroscience.* 2010;157(1-2):9–17.
194. Manneras L, Jonsdottir IH, Holmang A, Lonn M, Stener-Victorin E. Low-frequency electroacupuncture 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.
195. Manneras L, Cajander S, Lonn 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.
196. 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.
197. Noguchi E. Acupuncture regulates gut motility and secretion via nerve reflexes. *Autonomic Neuroscience.* 2010;156(1-2):15–18.
198. 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.
199. 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.
200. 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.
201. Burnstock G. Acupuncture: a novel hypothesis for the involvement of purinergic signalling. *Medical Hypotheses*. 2009;73(4):470–472.
202. 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.
203. 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.
204. 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
205. 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.
206. Li P, Tjen-A-Looi SC, Longhurst JC. Nucleus raphe pallidus participates in midbrain-medullary cardiovascular sympathoinhibition during electroacupuncture. *The American Journal of Physiology.* 2010;299(5):R1369–R1376.
207. 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.
208. 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.
209. Guo ZL, Li M, Longhurst JC. Nucleus ambiguus cholinergic neurons activated by acupuncture: relation to enkephalin. *Brain Research.* 2012;1442:25–35.
210. 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.
211. 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.
212. 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.
213. 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.
214. 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.

215. 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
216. 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
217. Kathleen K.S., Huia Jing, Liua Ovid, et al. The integrated response of the human cerebrocerebellar 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
218. 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
219. 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.
220. 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
221. Bai, L, Yan. H, Li L, Qin, W, Chen P, Liu P, Gong Q, Lui Y, Tian J. Neural specificity of acupuncture stimulation at pericardium 6: evidence from an FMRI study. J Magn Reson Imaging. 2010 Jan, 31(1):71-7. doi:10.1002/jmri.22006
222. 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
223. 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
224. 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.
225. 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
226. 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
227. 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
228. 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.
229. 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