

Dysautonomia: Common Symptoms of Parasympathetic and Sympathetic Dysfunction are Due to Poor Cerebral Perfusion: A Review and Understanding of Cranial Anatomy and Parasympathetic Physiology, Part I – The Cortex and Midbrain

by

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ABSTRACT

The Central Nervous System includes Parasympathetic and Sympathetic nervous system (P&S, *aka.*, Autonomic Nervous System) centers. They tend to be the command-and-control centers for the P&S systems. As a result, not only does poor cerebral perfusion affect the peripheral P&S systems, it also affects the central systems. To improve the understanding of the effects of poor cerebral perfusion a review of the autonomic anatomy of the central nervous system is offered. This is the first of a two-part review of cranial anatomy as is related to the P&S nervous systems. Here in Part I the focus is the Cortex and the Midbrain, the command centers of the P&S nervous system.

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INTRODUCTION

The Parasympathetic and Sympathetic (P&S) nervous systems are the primary connection between the brain and the heart or the mind and the body. It may manifest as simply as “butterflies in the stomach” caused by nervousness. Nervousness, such as with public speaking, is a mental phenomenon. Yet, among other responses, it manifests as increased gastrointestinal (GI) motility as part of the “flight-or-fight,” stress response. This begs the age-old question, which is more important, the brain or the heart? The truthful answer is: without the brain the heart does not work well and without the heart the brain will not work well. In other words, without proper perfusion from the heart and vasculature the brain (short hand for the Central Nervous

System) does not function well, and without a proper signaling from the brain, via the P&S systems, the heart and vasculature do not function well.

Proper cerebral perfusion is crucial, as the brain consumes about 70% of the body’s resources while an individual is at rest, and up to 85% when an individual is active, regardless of whether mentally or physically active. Cerebral perfusion does not only include the brain proper, but all structures above the heart, and may include the heart as well, depending on the portion of the autonomic nervous system that is dysfunctional. To be specific, cerebral perfusion includes (1) the Cranial Nerves, the eyes (the retina is actually part of the brain), ears (both auditory and vestibular), nose (olfaction), mouth (taste, tongue,

pharynx, and larynx), and face (tactile sensations); (2) the muscles between the shoulders and up the neck (the “Coat Hanger muscles”); (3) the brain stem (Medulla, Pons, & Cerebellum); (4) the midbrain (Thalamus and Hypothalamus); and 5) the Cerebrum; as well as the cortex.

A common effect of poor perfusion is the damaged nerve effect. When nerves, including brain cells, are damaged they over-react. In the body this is how the periphery signals to the brain that there is damage and results in the perception of pain. In the central nervous system, it may cause motor or sensory anomalies (*e.g.*, hyperactivity or hyper-sensitivity). P&S dysfunction may lead to poor perfusion. The two primary dysfunctions that lead to poor cerebral perfusion are (1) Sympathetic Withdrawal (SW, an α -adrenergic insufficiency [1]) that underlies Orthostatic dysfunction and pooling of blood in the lower extremities, and (2) Parasympathetic Excess (PE, an abnormal Parasympathetic response to a Sympathetic challenge – including stress [2]) that underlies (pre-clinical) Syncope. Both dysfunctions cause poor blood flow, especially to the brain and all structures above the heart, which is known as poor cerebral perfusion and the constellation of symptoms that may accompany it, including: difficult to control BP, or blood glucose, or hormone level, or weight; difficult to describe pain syndromes (including CRPS); unexplained arrhythmia (palpitations) or seizure activity (myoclonus); temperature dysregulation (both response to heat or cold and abnormal sweat responses); poor wound healing; symptoms of depression, or anxiety, or ADD/ADHD, or OCD; fatigue; exercise intolerance; sex dysfunction; sleep or GI

disturbance; lightheadedness, including POTS or Orthostatic Intolerance or Orthostatic Hypotension, or Syncope; cognitive dysfunction or “brain fog;” frequent headache or migraine; vision, or hearing, or vestibular, or taste, or smell, or abnormal facial tactile sensations; and abnormal immune function, including auto-immune-like disorders (especially ones that do not have auto-antibodies).

In some of the brain circuitry, the Parasympathetics use Nitric Oxide as a neurotransmitter. Nitric oxide is primarily produced by Epithelial cells throughout the body including the blood brain barrier. In general, Nitric Oxide is known as the universal messenger, made in ubiquitous quantities to signal both defense mechanisms blocking harmful substances from entering the body and the mechanisms that permit helpful substances to enter the body. As such it is involved in many processes, including: detoxification and the Urea Cycle, tissue regeneration, blood flow, prevention of atherosclerosis, and regulation of inflammation, and oxidation. [13]

Herein we will focus on the Cranial Nerves, Cortex, and Midbrain; with the midbrain being the command center of the P&S nervous systems. In Part II we will discuss the Brain Stem and the Spinal Cord, with the Brain Stem, specifically the Medulla Oblongata as the control center of the P&S nervous systems. Note, without treating SW or PE (including both together if both present together – treating SW moves blood to the abdomen and treating PE helps the heart to pump blood more efficiently) including both if needed, proper cerebral perfusion may not be achieved [3,4]. Both are needed: 1) relieving SW moves blood to

the abdomen so the heart may pump easier, and 2) PE needs to be relieved to efficiently pump blood to the head. Also note, most symptoms of poor cerebral perfusion are due to dehydration, including not enough water or electrolytes, or too much sugar, sugar substitutes, caffeine or alcohol or diuretics, all of which will dehydrate.

CRANIAL NERVES

Poor perfusion of the Cranial Nerves (CN, as they are above the heart) may lead to:
CN I) smell dysfunction (Olfactory nerve),
CN II) vision dysfunction (Optic nerve), CN III) muscles around the eye or eyelid muscle dysfunctions (Oculomotor nerve), CN IV) eyeball muscle dysfunction (Trochlear

nerve), CN V) facial sensory or motor dysfunctions (Trigeminal nerve), CN VI) eyeball muscle dysfunction (Abducens nerve), CN VII) facial expression muscle and taste dysfunctions (Facial nerve), CN VIII) balance and hearing dysfunctions (Vestibulocochlear nerve), CN IX) swallowing and taste dysfunctions (Glossopharyngeal nerve), CN X) dysfunctions of most of the Parasympathetic nervous system outside the brain (organs located between the base of the skull to the pelvis, including blood flow to the brain; the

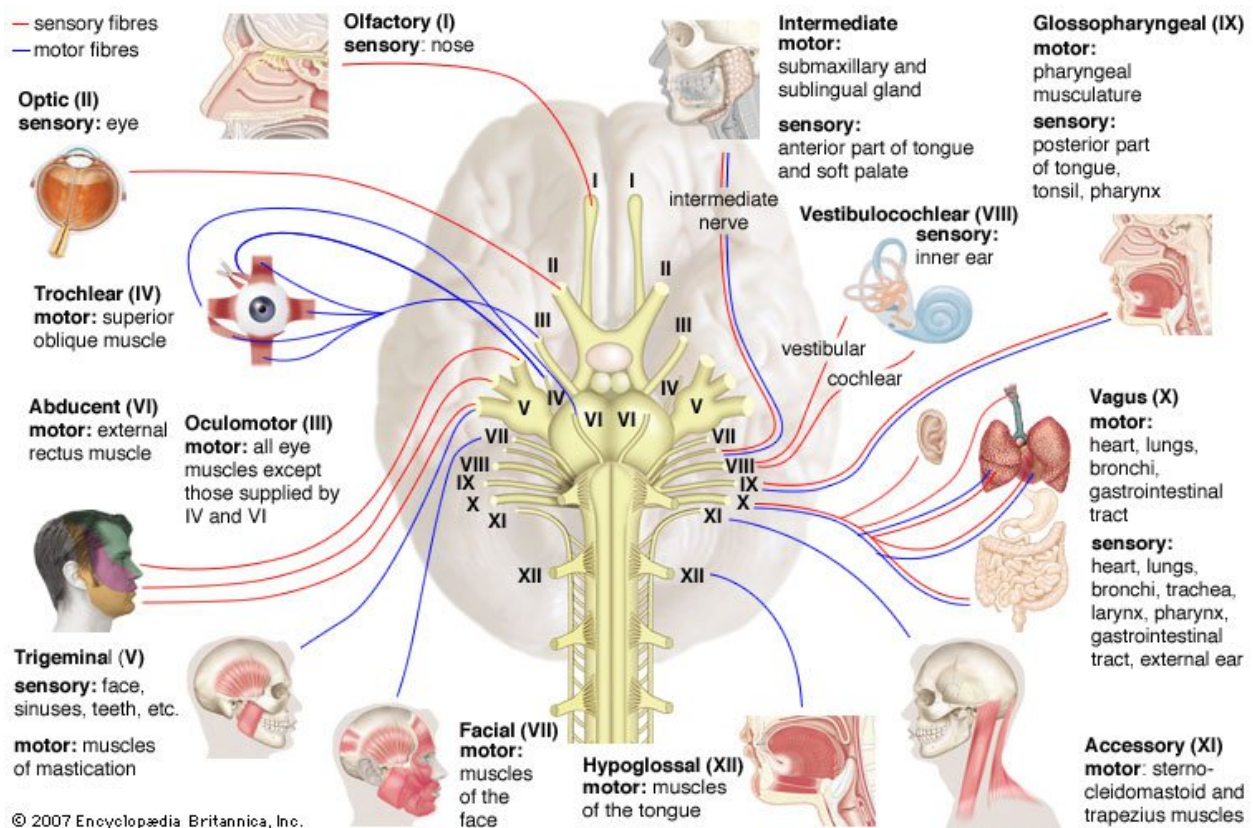


Figure 1: The Cranial Nerves (I–XII) and their areas of innervation. [5]

Vagus nerve), CN XI) neck muscles dysfunctions (Accessory nerve), and CN XII) speech and swallowing dysfunctions (Hypoglossal nerve); see Figure 1.

The cranial nerves pass through small openings in the skull. These openings are lined with a relatively thin layer of tissue to buffer the nerves from the rough bone. With inflammation, not only are the nerves themselves inflamed and susceptible to compression from the inflammation, but the lining that buffers the nerves from bone may also become inflamed further compressing the nerve. In some cases, the capillaries in the tissue lining may transmit the pulsing of the heart to the compression causing the compressions to feel like they are coming from the structures the cranial nerve innervates. Since everyone is different and these openings are therefore a little different, some people may have different nerves affected and affected in different ways.

MIDBRAIN AND CORTEX

Stress is a sample cortical phenomenon that is transmitted to the body through various neural and hormonal pathways (see Figure 2), largely involving the P&S nervous systems (which also helps to control the hormones). For example, the feeling of butterflies in the stomach may be caused by stress. What is the connection? It is part of the “flight-or-fight” response. Consider a snake that has just consumed a meal. If even the shadow of a cut out of a bird of prey passes over the snake it will disgorge the meal so that it may flee the predator faster; “lighten the load,” as it were. This same reaction is innate in humans (see Figure 3). Stress may cause GI motility to react in a fight-or-flight manner. In addition

to stress, other functions to coordinate cortical and bodily responses are also mediated through the midbrain, especially the Hypothalamus, via the P&S systems (see

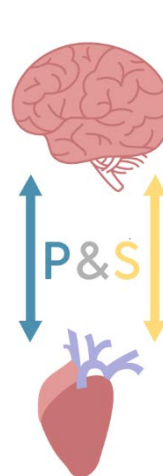


Figure 2), including feeding, voiding, circadian rhythms, hormonal cycles, growth, healing, immune responses, detoxification, fluid balance, blood pressure, heart rate, histamine and inflammatory reactions, blood sugar levels, pain, and more.

The P&S nervous systems operate without conscious control, it is primarily regulated by the Hypothalamus and the Medulla Oblongata with input from the Limbic system and other regions of the Cerebrum (see Figure 2). The afferent components of the P&S systems consist of general visceral sensory neurons.

As depicted in the “Balance Under Stress” diagram below, the Hypothalamus and Amygdala include projections to the Medullary Brain Stem P&S nuclei. These projections modulate cardiac, respiratory, gastrointestinal, glandular (*e.g.*, adrenal and corticosteroid), and vasomotor centers. Through these projections, the Medulla mediates P&S and involuntary activities, *e.g.*, ventilation, plasma pH, HR, and BP. BP is mediated via Sympathetic drive, the vasomotor center, baroreceptor activation, and vasoconstriction. In the Brain Stem, the Nucleus Tractus Solitarius, Nucleus Ambiguus, and Dorsal Motor Vagal Nucleus are important structures involved in efferent and afferent Vagal (Parasympathetic) activity. The Nucleus of the Solitary Tract is

a site of integration of both the afferent and efferent neural regulation of the cardiorespiratory and immune systems [6,7]. The lateral Hypothalamus and the Amygdala with the Basolateral Nucleus generate inhibitory control over Parasympathetic structures in the Brain Stem during stressful events and in anxiety. To provide balance, the medial Prefrontal Cortex and the Orbitofrontal Cortex facilitate Vagal output and inhibit the Rostral Ventrolateral

Medulla. Finally, emotions, including anxiety, depression, anger, and love, effect thoracic and visceral organs via projections from the Dorsal Motor Vagal Nucleus and Nucleus Ambiguus, primarily via the Vagus Nerve, and the projections from the Nucleus Tractus Solitarius and Rostral Ventrolateral Medulla, primarily via the Sympathetic Chain.

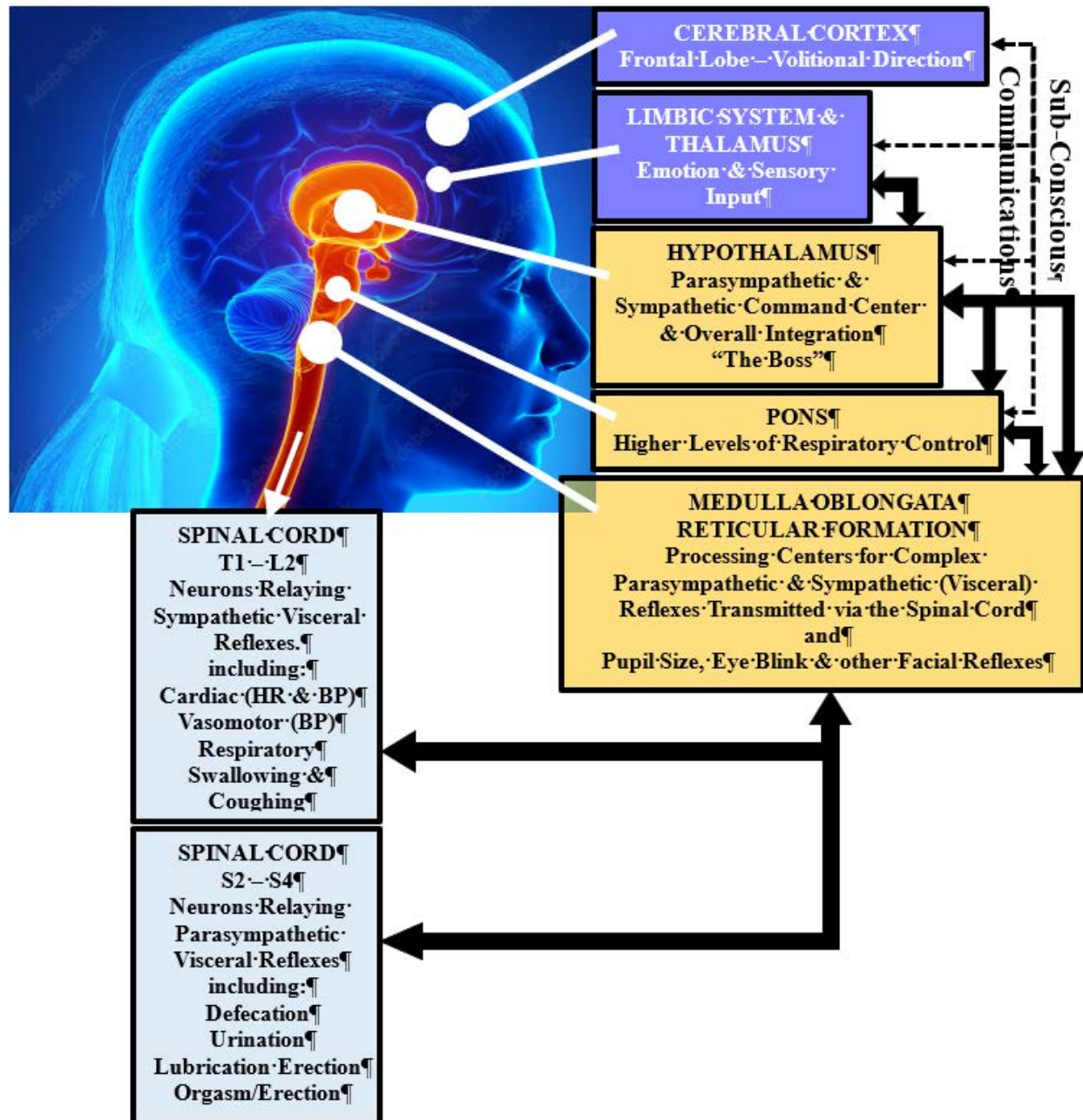


Figure 2: Hierarchy of P&S control and coordination. Figure of female adapted from [8].

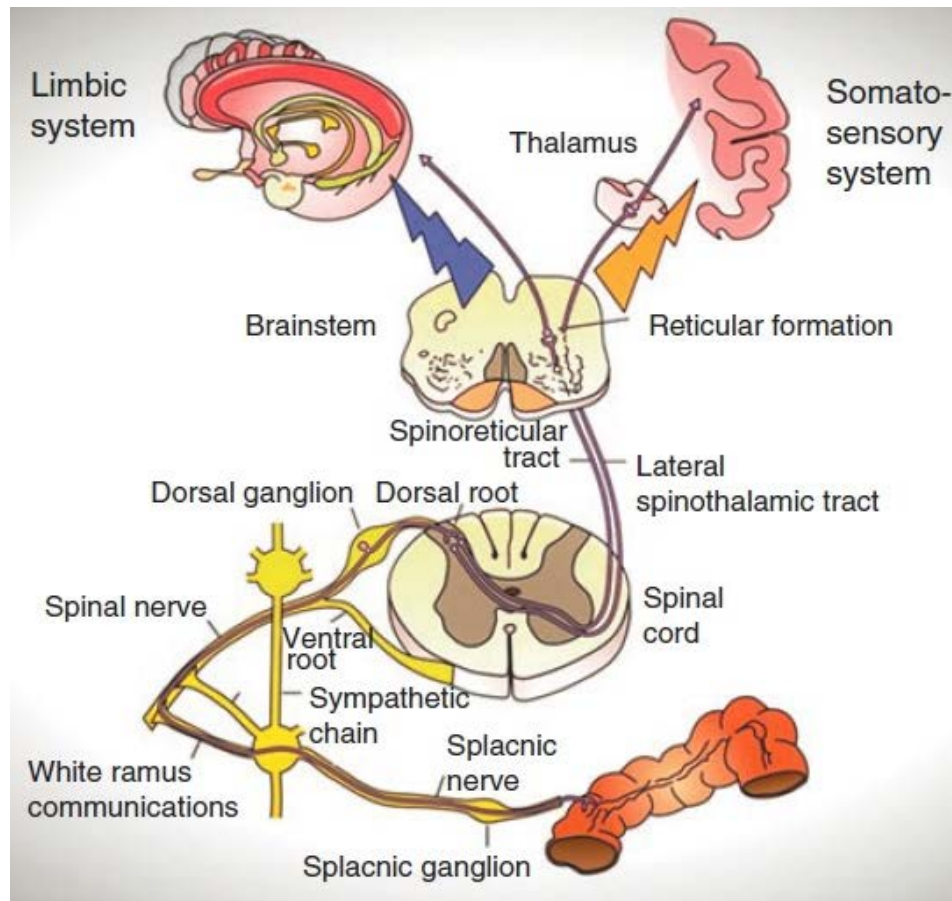
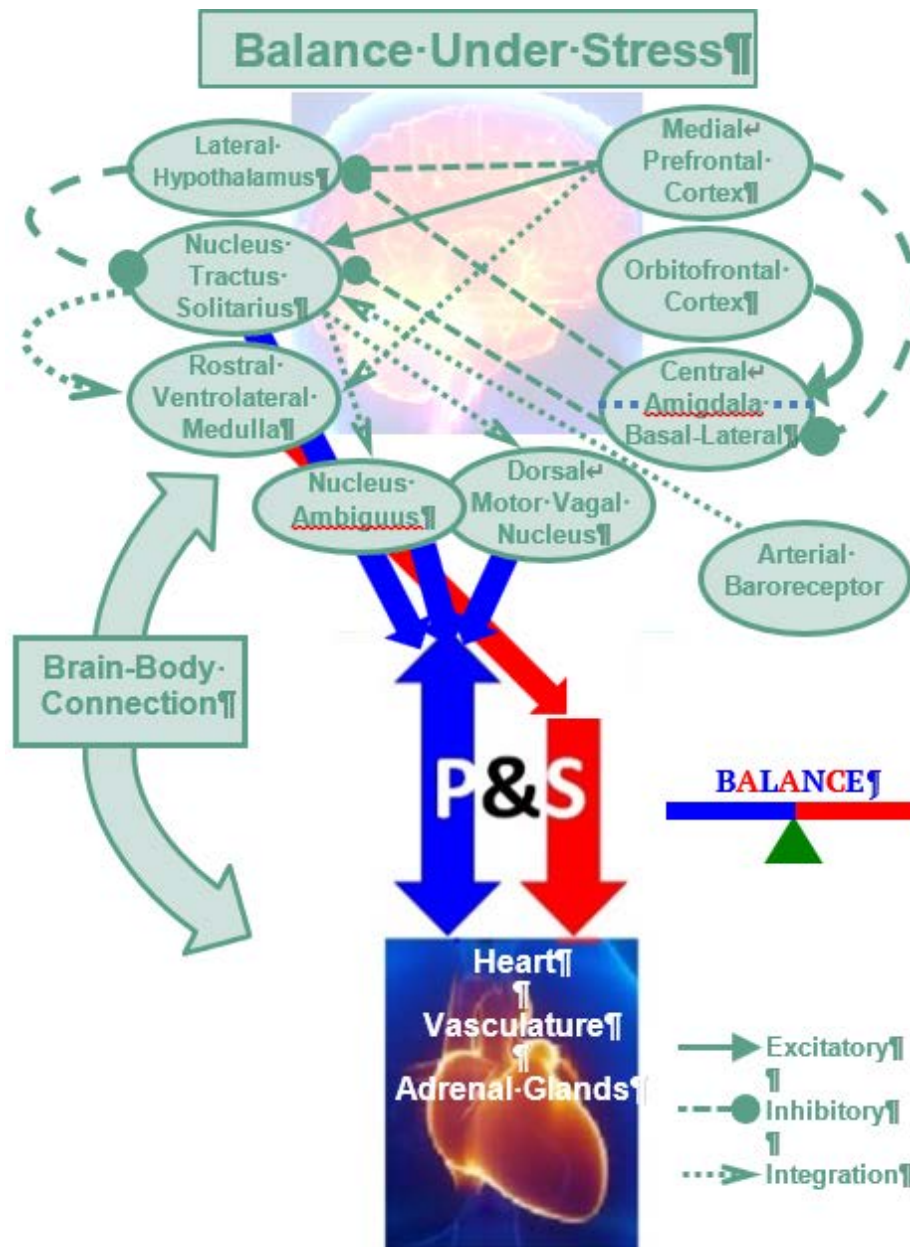


Figure 3: The Somatosensory and Limbic pathways for abdominal pain, highlighting the Sympathetic connections. These connections underline the link between emotional and digestive responses. [Modified with permission from Cardinali, 9]



Parasympathetic (Vagal) control and coordination of the immune system is depicted in Figure 4. The is the basis of the effect of severe or prolonged immune activation (another type of stressor) as a possible cause of Parasympathetic Excess (PE). The Parasympathetics innervate the intestine, spleen, and liver, and bidirectional

neuroimmune signals coordinate brain (Central Nervous System) and peripheral immune responses (including Mast Cell Activation). Circulating immune signals (e.g., cytokines and chemokines) and bioenergetic signals (e.g., endogenous

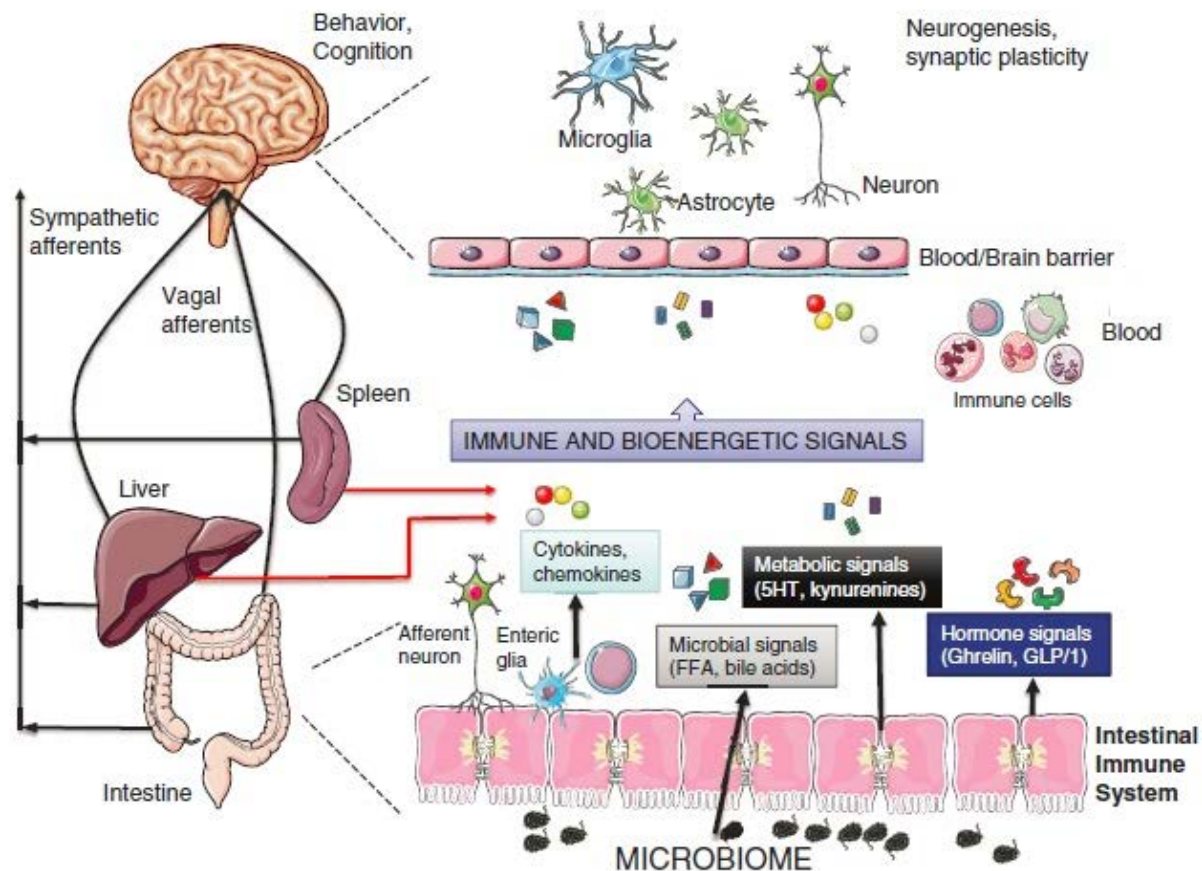
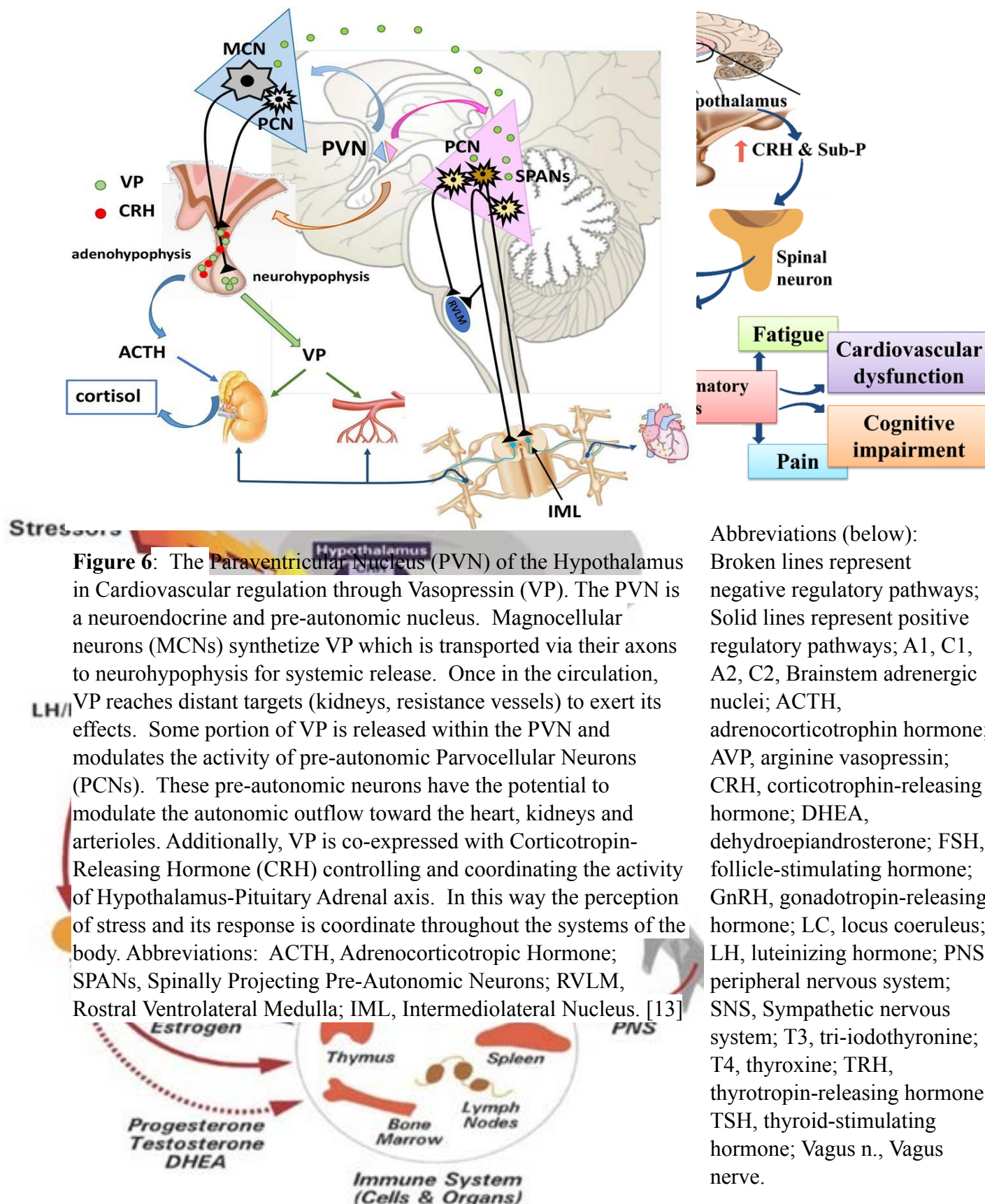


Figure 4: The basis of the effect of the microbiome on brain function as mediated through the P&S nervous systems. [Modified with permission from Cardinali, 7]

metabolites of microbial origin) may impact the brain microenvironment. This provides a rationale for the poor outcomes that accompany traumatic brain injury [10], including concussion.

Stress is arguably the greatest adversary of a patient diagnosed with autonomic dysfunction. Many stress responses are mediated through Substance-P pathways (Figure 5 [11,12]). Substance-P and its

preferred Neurokinin 1 (NK1) receptor has been found within brain areas known to be involved in the regulation of stress and anxiety responses. Also, emotional and mental stressors increase Substance-P efflux in specific Limbic structures such as Amygdala and Septum. The magnitude of emotional stress effects depends on the severity of the stressor. While emotional and mental (psychological) stressors are

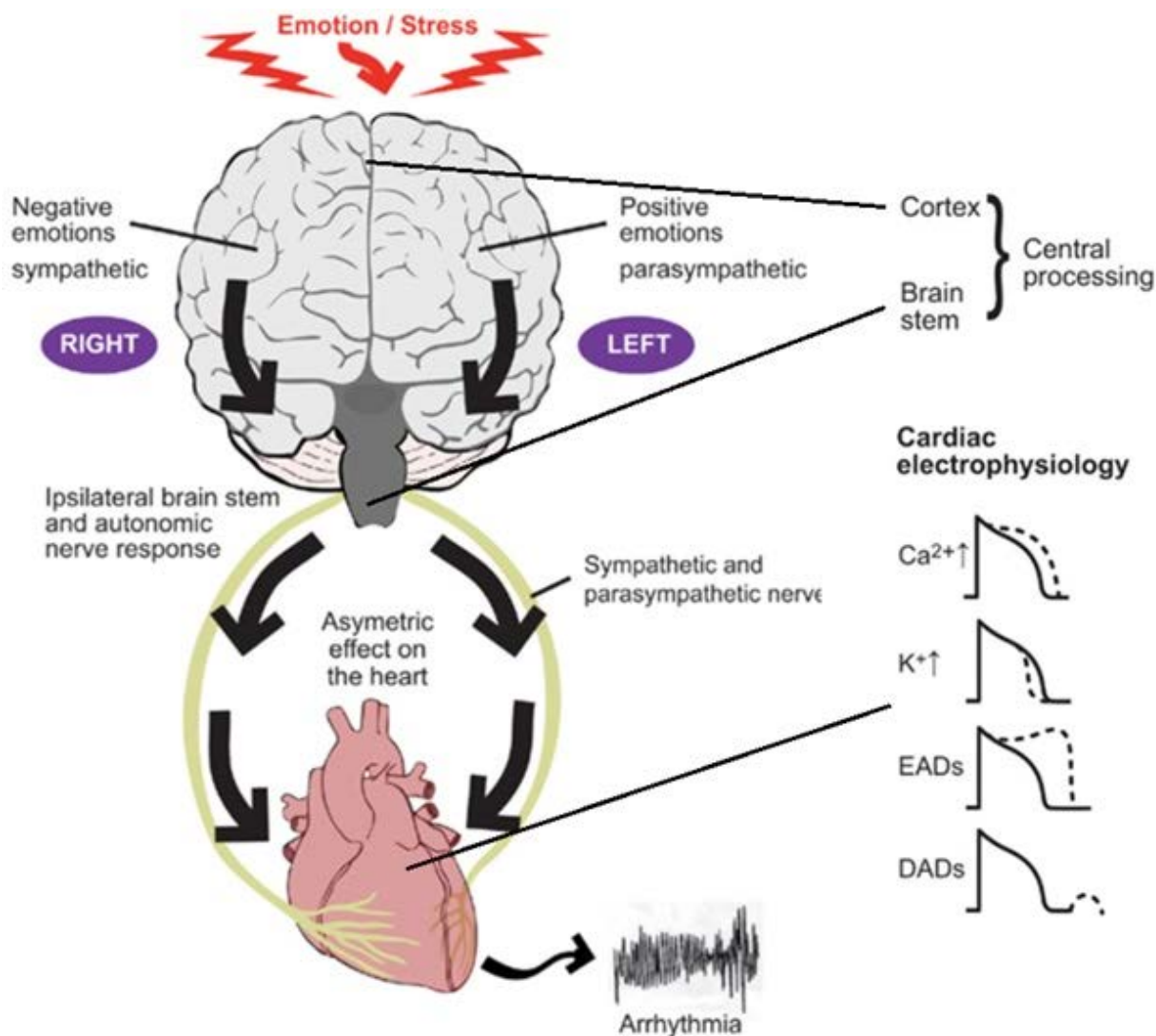


arguably worse than physical (physiological) stress, because you cannot run away from them, stress reduction is important in relieving autonomic dysfunction and its associated symptoms [13].

Another example of the Mind-Body connection from the Midbrain is the role of the Paraventricular Nucleus (PVN) of the Hypothalamus (see Figure 6 [14]). The PVN is one of the most important autonomic control centers in the brain. It has neurons that play essential roles in controlling metabolism, growth, reproduction, immune, and other more traditional autonomic functions (*i.e.*, GI, Renal, and Cardiovascular control). The PVN controls BP and BP variability and thereby has a key role in regulating cardiovascular and osmotic homeostasis, including via the renal and vascular systems. In this way the PVN also controls stress through control of Cortisol levels by way of ACTH, for example. Via ACTH Catabolism, Tachycardia and Tachypnea,

increases in BP, redistribution of blood flow and immune-suppression are effected as a part of the stress (“Fight or Flight”) response (see insert below).

As depicted in the insert (below), ultimately, stress and emotions affect the heart. Just as there is a math v art dominance in the brain there is a Parasympathetic v Sympathetic (respectively) dominance in the brain as well [15,16,17,18]. Strong, prolonged or too many stressors eventually accumulate and may cause inappropriate cardiac electrophysiology leading to arrhythmia.



The next insert below summarizes the joint effects of stress on both the P&S systems and the HPA axis. This Neuroendocrine response to stress involves oxidative stress and Sympathetic Excess (SE, a β -adrenergic response), leading to inflammation and activation of the Renin-Angiotensin-Aldosterone System (RAAS), leading to endothelial dysfunction.

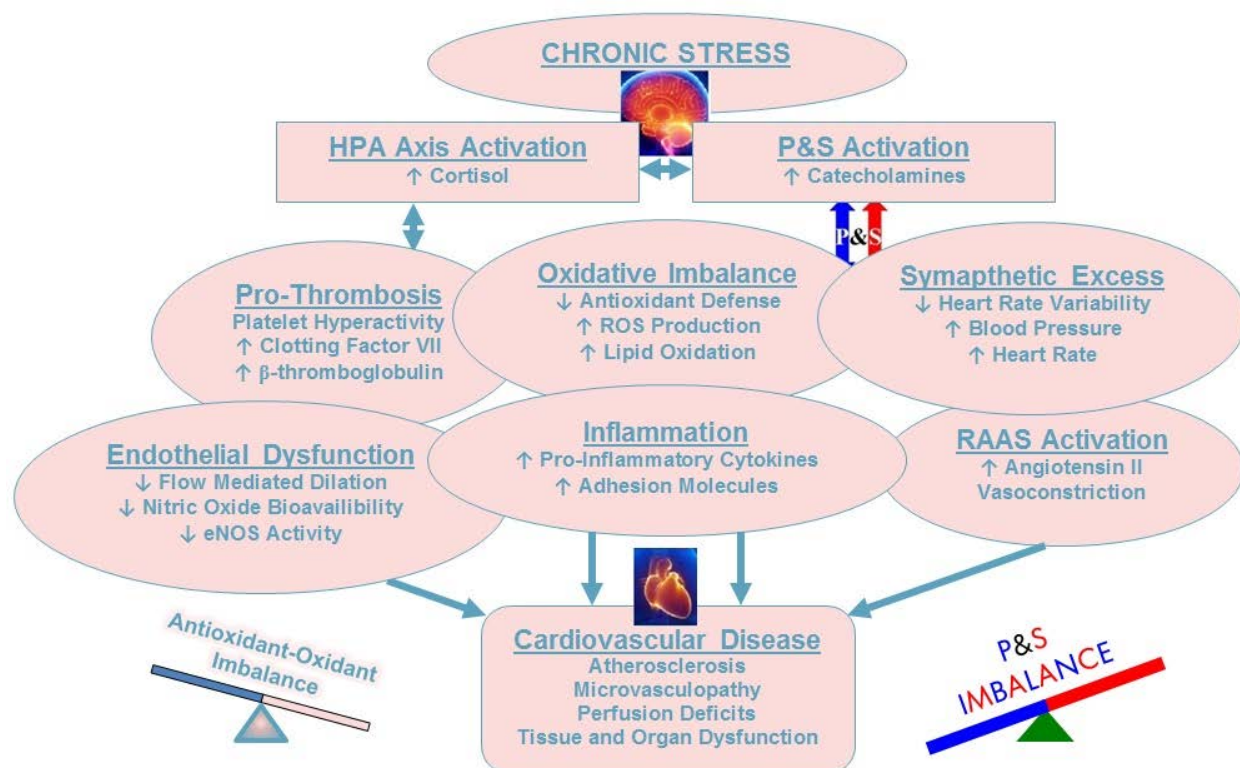
Stressors and irritants and other conditions may cause histaminergic reactions, which are also mediated through the mid-brain (see Figure 7) via the P&S systems effecting

mast cell release and histamine release, respectively. Often we have found Mast Cell Activation Syndrome to be a function of PE and secondary SE. Where PE releases too many Mast Cells and causes SE. The SE releases too much Histamine from each and every Mast Cell causing an over-amplification of Histamine release. In some female patients, this overamplification is found to be a root of their womens' health issues, including heavy and prolonged flows, sometimes with clots, and potentially leading to Dysmenorrhea, Endometriosis, PCOS, etc. Some of these women present

with PE and secondary MCAS simply from more than two pregnancies, which often includes one or more miscarriages, or other significant or chronic stressors. The underlying Mast Cell over-activation may be treated with H1 & H2 blockers while the PE that underlies that is relieved.

Many patients with autonomic dysfunction, including POTS and other Orthostatic dysfunctions have a low blood volume when

formally assessed [19,20,21]. It has been reported [9,22,23] that irregularities in the Renin-Angiotensin-Aldosterone System (a portion of the P&S nervous system) with low Aldosterone may contribute to abnormal Renal sodium (Na^+) handling and Hypovolemia (circulating and fluid volume) in POTS [see Figure 8, “Chronic Hypovolemia” 24, Public Domain].



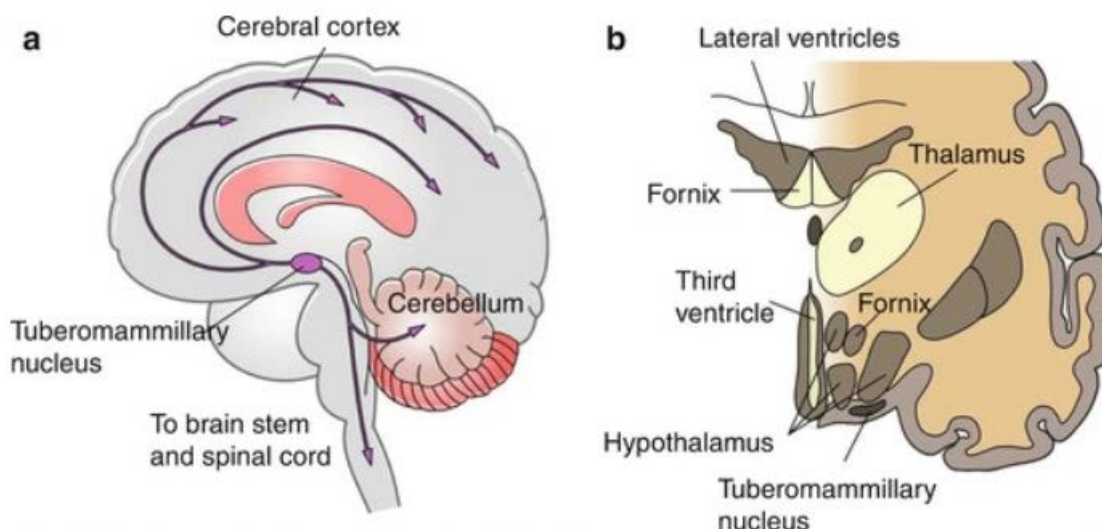


Figure 7: Histaminergic projections originating in the Tuberomammillary Nucleus (TMN): a) Distribution in a sagittal plane, and b) Hypothalamic locations of the TMN. [Modified with permission from Cardinali, 7]

As we have learned from Critical Care Medicine [25], the Parasympathetics are primarily responsible for proper tissue perfusion throughout the body. A long Valsalva maneuver (> 20 seconds) is a prime example. Chronic hypovolemia (see Figure 8) causing poor tissue perfusion may be a cause of PE. In this culture, most drinks consumed contain caffeine, sugar or artificial sweeteners, or alcohol. All of these drinks dehydrate and alcohol also vasodilates. This is exacerbated by the numbers of patients diagnosed with Hypertension that are prescribed diuretics. As a result, the majority of patients with autonomic dysfunction are dehydrated and require more water with electrolytes, specifically Sodium (if BP is normal or low) or Potassium (if BP is high). The (flavored) salt for Sodium or fruits and vegetables for Potassium is required to be dosed every two hours to help maintain the water in blood vessels and not in the kidneys.

Note: recently most providers state that they do not know the cause of POTS, and it is likely true that they do not. It is well known

that $\frac{1}{3}$ to $\frac{1}{2}$ of all POTS patients have comorbid Vasovagal Syncope. The problem is that except for P&S monitoring it is not possible to differentiate the two. As a result, these providers only treat the symptoms of Tachycardia. This presents another problem. The Tachycardia is a compensatory mechanism causing the heart to work harder to compensate for blood pooling in the lower extremities. Tachycardia treatment may make the blood pooling worse, and ultimately exacerbating the symptoms of POTS, furthering the chronic hypovolemia.

Autonomic dysfunction and associated chronic hypovolemia may result in tremors. If there is no evidence of seizure activity from the EEG, then it may not be Epilepsy. Rather it may be Myoclonus. The cortical hemisphere dominance, myoclonus, and other effects of autonomic dysfunction in the central nervous system, *e.g.*, type, location, or source of migraine, such as visual migraines, or light sensitivity, may also be due to the distribution and source of P or S dysfunction effecting one or the other

Chronic Hypovolemia

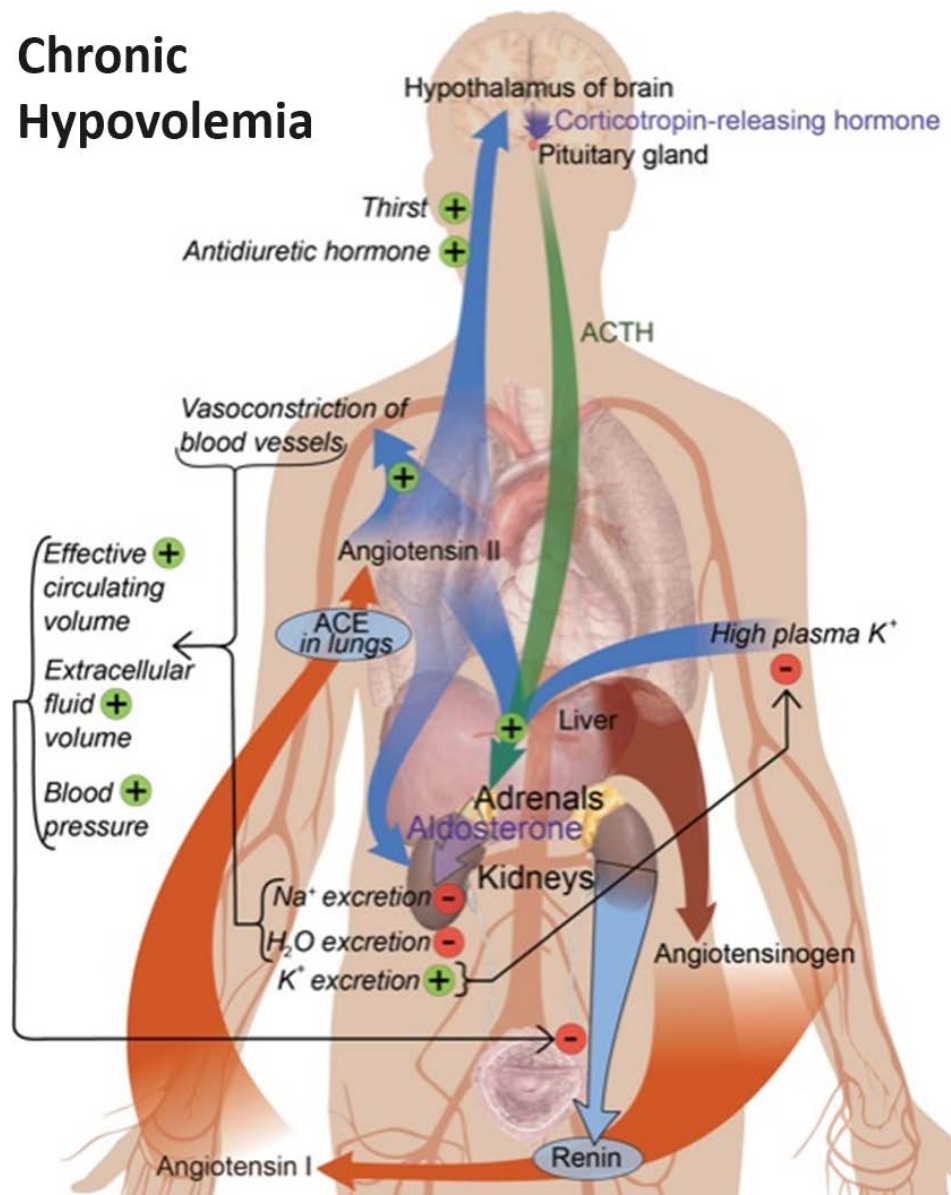
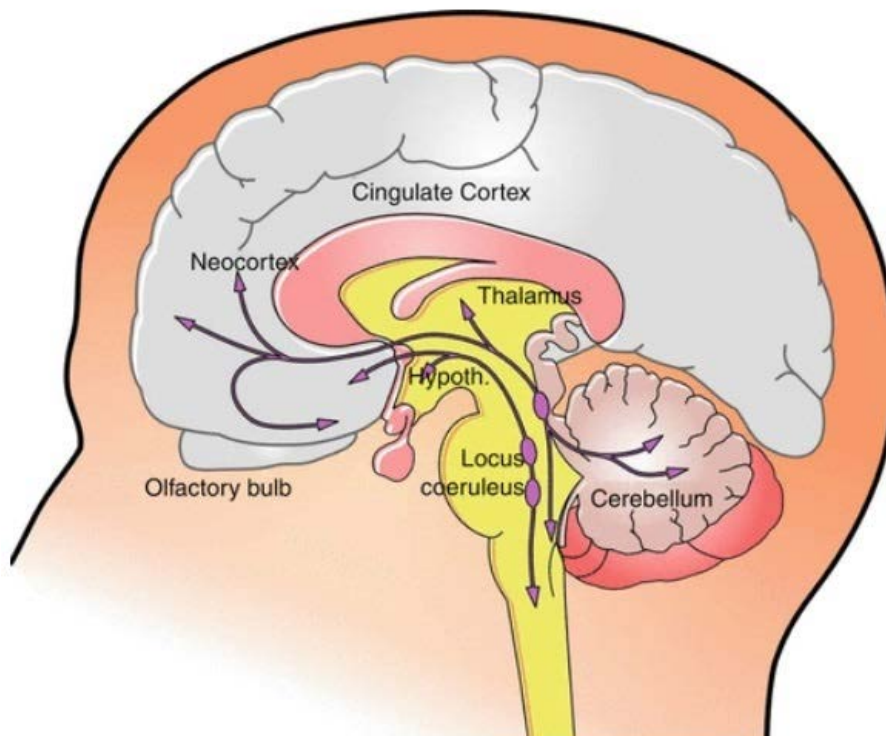
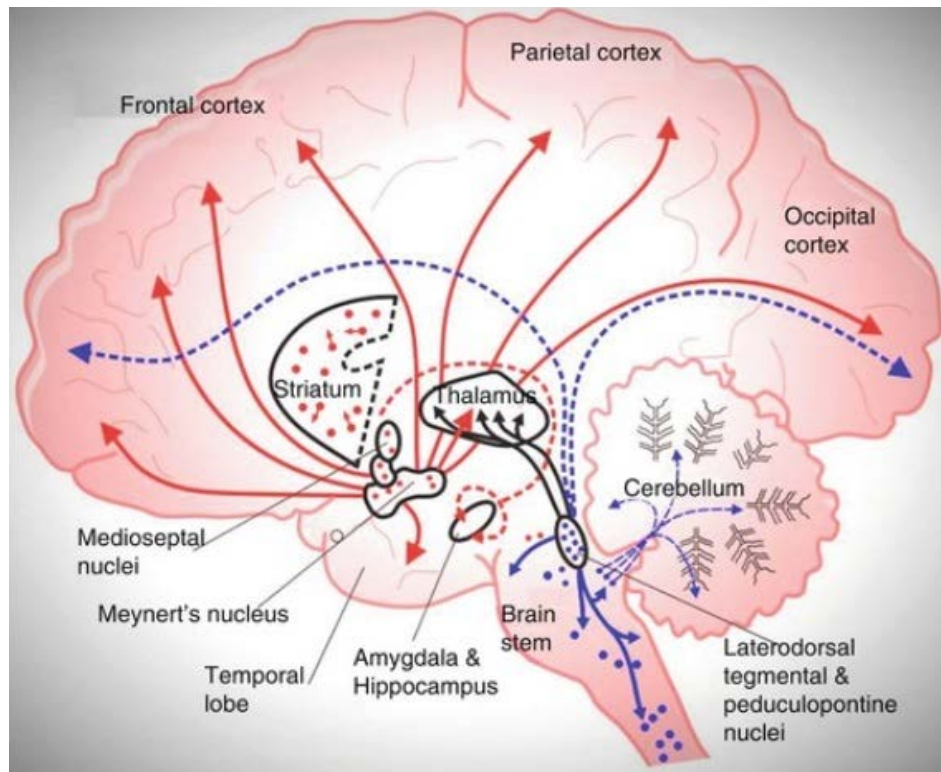


Figure 8: Projections involved in compensating for hypovolemia.

hemisphere. The P&S carry information throughout the brain as well (the next two inserts):

The next insert (below top) depicts principle Cholinergic projections from the midbrain to the Cortex [Modified with permission from Cardinali, 7]. The following insert (below

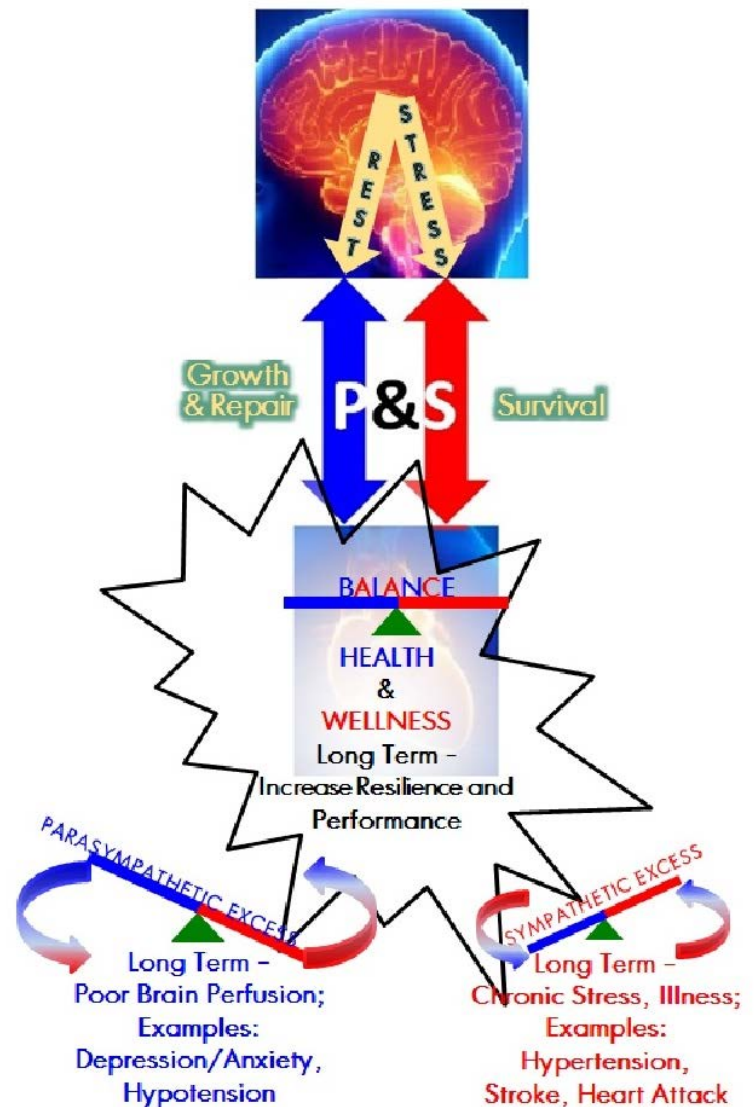
bottom) principle Noradrenergic projections to the Cortex from the Reticular Formation (the tegmentum) in general and more specifically from the Locus Ceruleus and project to the Cerebral Cortex, Limbic System, Basal Ganglia, Thalamus, and Hypothalamus within the brain [Modified with permission from Cardinali, 7]



CONCLUSION

While the focus herein has been stress, stress comes in all forms. In addition to the stressors mentioned above, there are stresses due to sleep difficulties that arise from Cortical and Midbrain sources including those due to Circadian Rhythm disturbances, Melatonin and Serotonin imbalances, and vision deficits [13]. Trauma, severe or prolonged stress both physical or mental, may lead to PTSD where the memory of the trauma, a cortical stimulation, triggers the stress response [13]. COVID and even the COVID vaccine, has proven to be a severe stress in some people leading to PTSD-like P&S dysfunction known as Long- or Post-COVID syndrome. In fact, Long-COVID and PTSD have the same Autonomic fingerprint (PE with SW and secondary SE), leading to the same constellation of possible symptoms [26]. Even healthy stressors, such as exercise and food when excessive, become unhealthy stressors and trigger imbalance. For example, the Hypothalamus regulates appetite, nutrient consumption and energy balance, with influences on hunger and via the P&S systems controls food intake (GI motility), Insulin production (Pancreas), Leptin production (Adipose tissue, influencing satiety), and body weight regulation (Melanocortin systems). [27]. The insert, right, indicates the need for a proper balance between stress (activity) and rest, and the long-term indications of too much of either. Health and wellness are based on this proper balance.

There are seven key disorders that are symptoms of inappropriate P&S responses or balance, including disorders of: 1) HR (*e.g.*, unexplained arrhythmias), 2) BP (*e.g.*, difficult to managed Hypertension and



Labile Hypertension), and 3) blood glucose (*e.g.*, hypoglycemia and diabetes-like syndromes); 4) abnormal inflammatory (including auto-immune syndromes, especially those with no known auto-antibodies) and 5) histaminergic responses (including MCAS, Celiac Disease, and unexplained allergies, rashes, or hives); and 6) amplified pain (including CRPS) and 7) anxiety-like symptoms (*e.g.*, depression-anxiety syndromes, Bipolar Disorder, and symptoms of the various Anxiety disorders). These, along with lightheadedness

(Orthostatic dysfunction, including POTS, or Syncope), fatigue (persistent or chronic, including ME/CFS [28]), brain-fog, memory and cognitive difficulties, headache (including from “Coat Hanger pain”), migraine, sleep difficulties, depression, and cranial nerve dysfunction, are all effected by poor cerebral perfusion and effect productivity.

In this way the whole body, every system, may be affected. This is why a comprehensive, multi-assessment system, full-body assessment is required to completely understand and diagnose P&S dysfunction and help the patient “connect the dots” and understand the cause of their condition; regardless of how complex it may be. Fortunately, and contrary to current opinion, all underlying P&S dysfunction is treatable and may at least restore quality of life and in many cases productivity. The symptoms of P&S dysfunction, including all

of the symptoms listed in the previous paragraph, are all curable, except in the presents of a certain small number of chronic diseases known to constantly pull the P&S systems out of balance (*e.g.*, Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorder and perhaps Diabetes). However, in these small number of chronic diseases, P&S dysfunction is still treatable and a normal quality of life and productivity is possible; in time. Herein Part I, we focused on the Cortex and the Midbrain, with the Midbrain being the command center for the P&S nervous systems. In Part II, we will focus on the Brain Stem and the Spinal Cord. In the Brain Stem, specifically in the Medulla Oblongata, we will find the P&S systems’ control center.

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