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Mathematical modeling the neuroregulation of blood pressure using a cognitive top-down approach

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Abstract
Background: The body's physiological stability is maintained by the influence of the autonomic nervous system upon the dynamic interaction of multiple systems. These physiological systems, their nature and structure, and the factors which influence their function have been poorly defined. A greater understanding of such physiological systems leads to an understanding of the synchronised function of organs in each neural network i.e. there is a fundamental relationship involving sensory input and/or sense perception, neural function and neural networks, and cellular and molecular biology. Such an approach compares with the bottom-up systems biology approach in which there may be an almost infinite degree of biochemical complexity to be taken into account. **Aims:** The purpose of this article is to discuss a novel cognitive, top-down, mathematical model of the physiological systems, in particular its application to the neuroregulation of blood pressure. **Results:** This article highlights the influence of sensori-visual input upon the function of the autonomic nervous system and the coherent function of the various organ networks i.e. the relationship which exists between visual perception and pathology. **Conclusions:** The application of Grakov's model may lead to a greater understanding of the fundamental role played by light e.g. regulating acidity, levels of Magnesium, activation of enzymes, and the various factors which contribute to the regulation of blood pressure. It indicates that the body's regulation of blood pressure does not reside in any one neural or visceral component but instead is a measure of the brain's best efforts to maintain its physiological stability.

Keywords: Mathematical modeling, physiological systems, blood pressure, autonomic nervous system.

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Introduction
The body's physiological stability is maintained by the dynamic interaction of multiple systems. These physiological systems regulate specific functions e.g. O2/CO2 levels in the blood; temperature; the absorption of minerals, vitamins and nutrients by the digestive tract; blood glucose; blood pressure; blood volume; elimination of wastes; etc. They influence the rates of reaction and extraction processes in the body. The ability of light to activate proteins is influenced by, and/or influences, these systems. Altered levels of minerals or ions e.g. of Magnesium or Sodium, permeate the cell membrane and alter the electrochemical characteristics of the cells and neurons i.e. their voltage gradients, and the firing ability of neurons.

Mono-chromatic light influences many of the body's physiological processes. The precise selection of light and/or colour selects those neurons which are sensitised and part of neurophysiological processes [1]. It influences the function of neurons in the brain and biological processes in the visceral organs e.g.

- it regulates the function of retinal photoreceptors [2, 3] and the flow of chloride through biological membranes [4]. This use of light has been able to halt brain activity in specific neurons using different colours [5, 6] and influence the timing of neural networks i.e. the firing of neurons. In halorhodopsin different colours stimulate different processes e.g.

green light initiates chloride transport and blue light induces proton pumping [1]. In addition, light influences synapse development [7].

- it activates gene expression [8] and mitochondrial DNA replication [9].

- it regulates the autonomic nervous system [10, 11] and the stability of the physiological systems.

- it regulates bilirubin metabolism [12, 13], the production of calcitriol [14, 15], and their various isomers. The action of light upon the skin produces calcitriol (1α,25 dihydroxyvitamin D_3) which is involved in brain function, synthesis of neurotransmitters, brain detoxification pathways, and has a significant neuroprotective and immunomodulatory effect [16, 17].

- it activates enzymes, which catalyse the body's function [18, 19], and influences the (i) production of Nitric Oxide [20] and subsequent regulation of blood pressure and lipid peroxidation; (ii) migration of stem cells [21]; (iii) rate of wound healing [22, 23]; (iv) rate at which proteins translocate to the cell membrane [18]; (v) function of the lymphatic system [24]; (vi) regulation of intercellular pH balance [25, 26]; (vii) blood flow [27] and heart rate [28]; (viii) sperm motility [29]; (ix) sexual function [30]; (x) immune function [31-33], etc.

The principle appears increasingly evident. Monochromatic light, received from the environment (and/or generated and transmitted in vivo), raises proteins to their activated state [19]. It may be essential for their subsequent reaction. The light emitted from such reactions explains the often observed, although hitherto unexplained, link between pathology and colour perception. The delivery of monochromatic light stimulates specific biochemical processes and regulates the function of the physiological systems [34, 35]. It synchronises the activity of groups of neurons [36] and their electrical impulses [37]. Whilst each physiological system has a primary function, by contrast most organs are multi-functional and are components in different physiological systems therefore instability in one system invariably influences the stability of other systems. Accordingly, measurements of visual perception reflect the actual rate of reactions between proteins and their substrates rather than their total level i.e. the rate of biophoton emission can be a measure of pathology.

Regulation of Blood Pressure

The prevailing understanding of blood pressure is within that of a *cardiovascular system* however there may be a need to revise this definition as (i) blood pressure, (ii) blood volume, (iii) breathing, and (iv) plasma glucose and other systems. Any mathematical model of blood pressure must take into account the various factors which directly and indirectly influence its function. Considering the issues from the perspective of a physiologically controlled system and fluid mechanics this suggests the need to include (i) neural regulation of blood pressure; (ii) feedback from baroreceptors located in the blood vessels; (iii) quality (and its viscosity), volume and pressure of blood; (iv) condition of blood vessels, their ability to handle the pressure, to ensure the smooth (parallel or turbulent) flow of blood, and to ensure a satisfactory supply of blood (and oxygen) to the brain (including partial occlusions) and visceral organs e.g. the heart; (v) influence of the autonomic nervous system (including sensory stimulii), the endocrine glands (pituitary, thyroid and adrenal) and the visceral organs which are part of the blood pressure system i.e. the heart, spleen and liver; (vi) nervous system feedback from the visceral organs and of neural components within this biofeedback system e.g. the cerebellum; and (vii) the extent of atherosclerosis.

The stability of each system involves the coordinated function of a considerable number of hormones [38] or substrates. In the case of blood pressure this involves e.g. catecholamines, aldosterone, oxytocin and vasopressin, acetylcholine, renin, angiotensin II, natriuretic peptides, vasopressin, nitric oxide, serotonin, GABA, ouabain, neuropeptide Y, opioids, bradykinin, thyrotropin-releasing factor, vasoactive intestinal polypeptide, tachykinins, histamine, corticotropin-releasing factor, melatonin, and fatty-acids.

Existing models largely exclude (i) the cumulative influence of memories, the impact of stress upon blood pressure, and the influence of the autonomic nervous system upon the function of neural structures; (ii) the role of the cerebellum; (iii) the influence of the body's biochemistry upon the firing of neurons and/or the reactivity of proteins with their substrates; (iv) and overlooks the inherent assumptions, limitations and errors in biochemical testing i.e. sampling time, variability between equipment, sampling errors, environmental context, genetic variations [39], patient age, etc.

To understand whether this revised understanding of physiological systems and mathematical model of blood pressure [11] withstands rescrutiny the objective herein is to consider each aspect of such a sophisticated mechanism.

Brain

The evidence suggests that stress-induced alterations to the hypothalamic pathways influence the regulation of short and long-term levels of sympathetic activity i.e. alterations in the levels of neurotransmitters and hormones increase sympathetic nervous activity and lead to a rise in blood pressure. The magnitude or longevity of this influence leads to altered homeostasis and changes to the homeostatic memory. This suggests that hypothalamic changes in hypertension are a link in an integrated response to sensory input, predominating as the kidney's impaired ability to excrete sodium and ultimately as high blood pressure. In particular, the medulla oblongata [40, 41] and dorsomedial hypothalamus influence the control of cardiovascular, respiratory and other physiological responses to acute stress [42]. Other neural structures or brain regions involved in regulating blood pressure include the amygdala [43, 44], periaqueductal grey matter [45], cerebellum [46, 47], pituitary, etc. In addition, electrical stimulation of brain centres can produce arrhythmias [48], ventricular fibrillation [49], etc. The level around which arterial pressure fluctuates or is regulated i.e. the 'neural set point', varies according to context. It is, therefore, maintained at a level which seeks to best maintain the body's physiological stability and its function.

Such observations may be adapted e.g. (i) cryogenic blockade of the forebrain, posterior hypothalamus, or Fields of Forel inhibits ventricular fibrillation [49]; (ii) electrical stimulation of the brain [45]; (iii) pulsed light therapies [34] activate the neural centres and influence high blood pressure; and (iv) meditation reduces blood pressure [50].

The Neuroregulation of blood pressure - The maintenance of 'normal' blood pressure regulates the supply of oxygen to the neural tissues and visceral organs [51]. It is essential to the body's stability and function: deviations being associated with cognitive impairment, migraine, dementia, stroke, diabetes mellitus, cardiovascular disorders, depression, sleep apnoea, etc. Within the medulla oblongata [40, 41] networks of neurons respond to signals received from baroreceptors and the autonomic nervous system [52, 53], and regulate blood pressure [54, 55]. They do so by changing heart rate or by contracting (or expanding) specific blood vessels in order to adjust the flow of blood. This is a rapidly adjusting dynamic system: blood pressure rising and falling almost instantaneously according to the body's needs.

What is measured as blood pressure by sphygmomanometer of systolic and diastolic measurements of blood pressure is the bio-physical manifestation of the prevailing biochemistry, and nervous and physiological structures. Blood pressure measurements, although invaluable in medical practice as an indicator of heart function, are the manifestation of the body's pathophysiology however an over-reliance upon blood pressure measurements may restrict consideration of the wide variety of contexts e.g. genetic [56-58], environmental [59-61], and gender [62, 63]. In addition, the level of cholesterol is influenced by the neuroregulation of the autonomic nervous system [64]. Altered neuroregulation may lead to different levels of ldl and hdl cholesterol thereby influencing blood viscosity and blood pressure.

The regulation of blood pressure by the autonomic nervous system is heavily influenced by stress [65] - Stress influences all aspects of cognition [66]. In particular, there is a link between cognition and pathology [67]. Stress is any combination of influences which exceeds the body's natural tolerance limits [68-70]. It influences the central nervous system [71,72]; subsequently induces biochemical dysfunction; and influences the regulation of organ function, and cellular and molecular biology [73]. It suppresses the immune [74] and endocrine [75] response(s). This generates reactive-oxygen species, which is manifest as oxidative stress [76] and subsequently as a ladder of pathologies [77] which progressively influence systemic stability. Accordingly any mathematical model of the physiological systems should consider all factors which influence the autonomic nervous system e.g. light and/or sensori-visual input.

Brain function includes brain physiology; regulation of the key physiological system and between physiological systems; sensory input, the storage (and retrieval) of memories, cognitive and behavioural consequences [78]. Sensory input, conveyed primarily by visual means, influences the hypothalamic-pituitary axis and other neural structures. The information received by the brain is processed and distributed via the neural networks to the visceral organs. Signal(s) returned to the brain indicate the body's physiological preparedness for activity and are processed and ultimately manifest as behaviour.

Regulation of blood pressure, and cardiovascular dysfunction, is influenced by stress and is now widely researched. Different stresses influence e.g.

- the measurement of blood pressure [79],
- the brain's ability to function [80] and regulate biophysical processes [81],
- the risk of hypertension has been linked to psychosocial factors [82],
- the occurrence of acute coronary events has been linked to emotional trauma [83],
- the occurrence of coronary heart disease has been linked to loneliness and/or social isolation [84, 85],
- the progression of carotid atherosclerosis has been linked to feelings of hopelessness [86],
- an increased risk of cardiovascular disease has been linked to distrust [87],
- the occurrence of coronary heart disease has been linked to anger [88, 89],
- dysfunction of the left ventricle has been linked to grief, bereavement and a broken-heart [90],
- the occurrence of coronary heart disease has been linked to stress in the workplace [91, 92],
- the risk of myocardial infarction in men has been linked to lack of exposure to sunlight [93],
- the lack of calcitriol in non-insulin dependent diabetes has been linked to the prevalence of cardiovascular disease [94].

In brief, stress is mainly due to the consequences of lifestyle e.g. poor diet/increased weight, lack of exposure to sunlight [93, 94], domestic and/or work-related stressors, etc. By contrast, and in support of the above, 'alternative' measures to reduce stress have been shown to reduce morbidity and mortality e.g. (i) the body requires a balanced supply of all key antioxidants. Vitamin deficiencies can be damaging to the body's function. An excess of vitamins can be as damaging as a deficiency. Vitamins C, D (calcitriol) & E influence blood pressure [95-97]. (ii) Light therapies [34], including exposure to natural sunlight, stimulate calcitriol production and regulate the body's function. (iii) Alternative approaches e.g. exercise [98], dietary interventions [99, 100], meditation [101, 102] and hypnosis, and stress management interventions [103] reduce morbidity and mortality [104, 105] and encourage normal physiological development [106]. (iv) Surgical approaches e.g. deep brain stimulation [45, 107, 108], have been developed which stimulate brain tissues.

Cognitive impairment is associated with the development of diabetes [109], the subsequent development of high blood pressure [110, 111, 115], heart dysfunction [112-114], increased age [115], and increased weight [116]. A decreased ability to deliver oxygen to the brain is a significant factor in the development of migraine, dementia [117, 118] and neurodegenerative conditions. Specific cognitive impairment e.g. to colour perception [109, 110], memory [116], hearing deficits [119, 120], olfactory deficits [121], etc; have been linked to cardiovascular deterioration or disease. There is a clear link between cognition and that of molecular and cellular biology [11, 122, 123].

Organs involved in the regulation of blood pressure: brain, pituitary, thyroid and adrenal glands, liver, heart, spleen, and blood and peripheral blood vessels

Visceral Organs

a. Apart from the pituitary gland which is the sole endocrine gland in the sleep system, the three primary endocrine glands are active in all other physiological systems. This indicates the value of sleep.

- Insufficient sleep i.e. too little (or too much) sleep or poor quality sleep, will suppress the function of the pituitary gland and influence the function of all other physiological systems.
- Light influences the function of the pituitary gland [124] and influences the function of the thyroid and adrenals i.e. the hypothalamic-pituitary axis.
- Reduced levels of calcitriol are suspected of lowering levels of parathyroid hormone and may increase blood pressure [97].
- Adrenaline produces rhythmic contractions of the spleen [125] and reduces the blood volume retained by the spleen.
- angiotensinogen levels in the liver are increased by thyroid hormone, corticosteroids, oestrogen and the enzyme angiotensin II.
- Overproduction of renin and its manifestation as high blood pressure has been linked to the production of cortisol [126].

Organs involved in the regulation of sleeping pattern: brain, pituitary gland, spinal cord, peripheral nervous system, ear and nose.

b. The quality of blood and the condition of blood vessels influence the body's function. Blood viscosity is the manifestation of its various components e.g. plasma glucose, fatty acids, cholesterol, etc.

- The greater blood viscosity the greater will be the energy required for the heart to pump blood through the lungs and to the brain.
- The slower will be the diffusion of oxygen through the blood and its subsequent absorption by haemoglobin i.e. the harder it will be to absorb oxygen.
- Increased blood viscosity will impair/slow ventricular filling [127].
- Increased levels of fatty acids, cholesterol, plasma glucose, etc; will increase blood viscosity and will slow the circulation of blood and its subsequent processing in organs e.g. pancreas, kidneys, liver, etc. This will inevitably slow metabolic rate, the generation of energy, etc. Some components have increased risk of precipitation and accumulation in the blood vessels and a greater 'stickiness' i.e. ability to adhere to blood vessel walls [128].
- Increased blood viscosity will slow the dissociation of proteins and substrates to and from their receptor sites thereby reducing rate of reaction and what we recognise as metabolic rate.
- Chronic and/or mild acidosis is the consequence of stress, lack of exercise and/or of obesity. It influences the ability to absorb minerals in the digestive tract.
- The condition of the blood vessels influences the ability of the heart to pump blood to the brain, failures of which can lead to haemorrhagic stroke [129].
- High levels of cholesterol and fatty acids may lead to atherosclosis [130, 131].

c. The heart pumps blood through the lungs and delivers oxygen to the brain. An adequate supply of oxygen is essential for the condition and function of all muscles and tissues in the body and, in particular, the musculature of the heart, liver and kidneys. The heart pumps the complete contents of the blood system around the body typically every c20 seconds. The pumping of blood through the brain, lungs and to the skin are essential for the body's ability to regulate: temperature, the ratio of CO_2/O_2, pH, and absorption of nutrients and minerals by the intestines; and the conditions which influence the rate of all enzymatic processes in the body.

d. The liver produces the hormone, angiotensinogen, which raises blood pressure in response to low blood pressure. The levels of angiotensinogen are influenced by the function of the endocrines. Blockages in the liver e.g. due to cirrhosis, (perhaps due to the congestion arising from fatty acid deposition) are likely to lead to portal hypertension.

e. The influence of the spleen upon the regulation of blood pressure is widely acknowledged although there is not an accepted understanding of its role [132-134]. There is a relationship between hypertension, retention of blood in the spleen [135] and the autonomic nervous system [136, 137]. The spleen's main function is to maintains a reservoir of blood and ensure the availability of blood in extreme circumstances [138], known as splenic extravasation, which influences blood pressure [139].

The inter-relationship between Physiological Systems

That there is a sophisticated inter-relationship between physiological systems is implicit. Each of the systems are characterised by its higher or lower function. They are dynamically inter-related i.e. higher function in one system is linked to higher (or lower) function in another system e.g. between blood pressure and breathing or between blood pressure and blood volume, however that they are independent systems is supported by noting that instability in one system is not necessarily supported by instability in other systems. The network of systems (see table 1) can reconfigure or compensate for instability in one system, OR can reconfigure at an anomalous level as the chronic condition (i.e. a pathological functional system). This may be responsible for baffling results e.g. the results from histopathological tests may be indicative of a medical condition yet the patient may not exhibit any symptoms, and vice-versa.

The regulation of blood pressure is influenced by, or influences, other physiological systems e.g. sleep [140-142], sexual function [143], breathing [144], elimination of fluids, pH, plasma glucose [145-147], etc. If overweight people with chronic kidney disease and/or cardiovascular disease have too little exercise this will influence (i) plasma CO2/O2 levels and pH; (ii) reduce adrenal function and inhibit the elimination of fluids (thereby influencing sodium levels and osmotic pressure in the cells); (iii) increase insulin resistance [148]; and (iv) destabilise sleeping patterns [149]. This is often the consequence of poor diet [128, 150, 151]. Moreover, low levels of exposure to natural sunlight will suppress the normal function of the pituitary gland and the generation of calcitriol in the skin.

Different medications act upon specific pathophysiologies e.g. beta-blockers moderate the function of the adrenals; calcium channel blockers reduce blood volume; diuretics act upon the kidney to reduce blood volume and levels of sodium; ACE inhibitors act upon the kidney and block the action of angiotensin-converting enzyme.

There is not a 100% association between chronic kidney disease and cardiovascular disease [152, 153]. High blood pressure occurs in an estimated 80% of patients with chronic kidney disease [154] although hypertension can occur without its occurrence, sometimes in quite extraordinary circumstances [155]. This suggests that regulation of blood pressure is subject to the influence of multiple variables, some of which have a greater or lesser influence according to their significance to each physiological system i.e. kidney dysfunction may be both the cause and the consequence of high blood pressure [156, 157]. This can only arise as a consequence of a dynamic, multi-systemic association.

Biochemical insufficiencies throughout the body will inevitably influence different aspects of the body's function e.g. factors influencing the gastrointestinal absorption [158] and/or retention of minerals [155, 159, 160], and perhaps also vitamins and/or hormones, and fatty acids. In particular, Magnesium deficits have been linked to a wide range of conditions including mitral valve prolapse [161, 162], coronary heart disease [163], hypertension [164], cardiac arrythmias, [165], congestive heart failure [166], diabetes mellitus [167, 168], migraines and epilepsy [169], fibromyalgia [170], asthma [171], attention deficit disorder [172, 173], pre-eclampsia [174], etc.

Lowered digestive pH reduces the levels of intestinal flora which are required to sustain the absorption of minerals at a satisfactory level. A Magnesium deficit is associated with the stress-mechanisms e.g. increasing the level of adrenaline and related corticosteroids, raising blood pressure [175]. Mg is required to activate muscle contractions e.g. in the heart, intestines, etc. Without an adequate supply of Mg the muscles and organs cannot function properly and remain in a contracted state. Lowered pH influences the nature and bioavailability of minerals: acid salts e.g. of phosphoric acid, bind with minerals (magnesium and calcium) in the digestive tract to form salts that are not absorbed [176]. The consumption of acidified soft drinks (pH typically 2.5) have been linked to the occurrence of chronic kidney disease [177], beer has a pH of typically 3.5.

The regulation of renin i.e. angiotensinogenase by the kidney and angiotensinogen in the liver is fundamental to the regulation of blood pressure. The reaction of these components produces angiotensin which causes constriction of blood vessels and raises blood pressure. There is a close association between the function of the endocrine glands and the renin-angiotensin system e.g. (i) angiotensinogen levels are increased by thyroid hormone, corticosteroid, oestrogen and angiotensin II levels; (ii) angiotensin stimulates the production of aldosterone from the adrenal cortex; and (iii) the pituitary hormone vasopressin influences the re-absorption of water into the blood (and hence the volume of urine). This influences the levels of minerals, in particular sodium and potassium, the osmotic pressure of the cells and intercellular communication. Accordingly any factors which influence the function of the endocrines will inevitably influence blood pressure. In particular, light activates enzymes; stimulates the production of pituitary hormones by the pituitary gland and calcitriol by the skin; the production of

Nitric Oxide [20] and the subsequent regulation of blood pressure and lipid peroxidation. Light is therefore an essential component in the body's regulation.

Table 1 Related physiological systems

Blood Glucose	Blood Pressure	Blood Volume	Breathing
Brain	Brain	Brain	Brain
Pituitary	Pituitary	Pituitary	Pituitary
Thyroid	Thyroid	Thyroid	Thyroid
Adrenal	Adrenal	Adrenal	Adrenal
Blood & pBV	Blood & pBV	Blood & pBV	Blood & pBV
	Heart	Heart	Heart
Liver	Liver		
	Spleen		
Pancreas			
Kidneys		Kidneys	Kidneys
Small Intestines			Small Intestines
			Lungs & Bronchi
			Skin
			Nose

Blood & pBV: blood and peripheral blood vessels

Discussion

This cognitive top-down model takes into account the cognitive influence of sensory input, memory and behaviour. It is based upon the concept that the body is a wholly biochemical organism and hence that all aspects of cognition must reflect the underlying biochemistry and bio-physical processes. It includes the influence of weight, age and sex upon the body's function: each pathology being expressed as a multi-component vector within a biomathematical matrix.

All mathematical models are estimates of varying precision therefore each cannot be expected to be entirely accurate. In this case we can dispute the accuracy of the predicted influence of weight and age. Furthermore it appears to be quite extraordinary that a cognitive technique could provide such huge amounts of data [178]. Every technique will have its benefits and weaknesses. Nevertheless the cognitive approach developed appears to offer a unique perspective regarding the diagnosis of disease, perhaps able to identify the nature and progression of disease more accurately than has hitherto been possible using conventional histopathological test methods.

This model considers that the brain acts as a neural matrix processing multi-sensory input from its external and internal environments, the consequence being its sensory output i.e. behaviour, and that the body acts as a visceral matrix: the organs being structured in arrays of synchronised and interdependent systems in which instability, the consequence of stress(es), is expressed as pathologies. Such methodology has been incorporated into a commercialised technology. As described, virtual scanning arises from a top-down cognitive mathematical model whereas most systems biology is based upon bottom-up biochemical models: the essential difference being that the cognitive model considers the top-down approach to be pre-eminent i.e. that systemic dysfunction is expressed as a biochemical dysfunction or pathology(s). Further evidence of this dynamic relationship is evident by noting how the cerebellum influences blood pressure yet paradoxically the body's function is able to continue when this neural component is removed. Moreover the cerebellum processes as much information as the rest of the brain. This can only be so if the cerebellum is involved in processing the feedback of data from the viscera to the brain i.e. the Purkinje cells of the cerebellum facilitate the feedback of data from all organs to the neural centres [179]. Accordingly, the loss of this function would enable the brain to continue to function although with progressive loss of regulation and onset of pathologies.

The cognitive approach recognises the influence of sensory input upon the neural matrix and subsequently upon the stability of the physiological systems and the autonomic nervous system. It has been a challenge for medical research to accept that stress, in its many and various forms, could alter the autonomic nervous system sufficiently to be responsible for raising blood pressure and the development of heart disease. It is reasonable to understand how the concept of a cardiovascular physiological system could have arisen. There is clearly a close association and interdependence of the physiological systems incorporating the coordinated function of the organs. In the case of blood pressure there is a close association with the regulation of blood volume and breathing but, as discussed, there is also the influence and inter-dependence of most other physiological systems. It may be too simplistic to consider that regulation of blood pressure is solely regulated by specific neural systems or components/organs [180] or of specific biochemistries e.g. the renin-angiotensin system, but instead that there is a complex system comprising neural regulation and biofeedback [81, 181] in which the renin-angiotensin system is most prevalent.

It is reasonable to conclude that there is a central regulating function but paradoxically it is also reasonable to conclude that such a mechanism does not reside in any one neural component or matrix of components but instead is a reflection of the brain's overall ability to maintain its function and/or stability [49] - and the function and stability of the various organ networks. The degree of function e.g. renal denervation [182, 183] or severe baroreceptor dysfunction [184], alters blood pressure and/or enables other regulatory systems to take over. Inhibition of other neural centres by the significant influence of sensory input, which is often discounted in orthodox systems biology, alters the degree of regulation.

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