World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

AUTONOMIC NETWORK AND BRAIN-HEART INTERACTIONS: A REVIEW FROM FUNCTIONAL PERSPECTIVES

***[1]Dr. Prashant Kumar Saini, [2]Dr. Poorvi Kulshreshtha and [3]Prof. Prashant M. Patil**

[1]Junior Resident, Department of Physiology, All India Institute of Medical Sciences, Rishikesh, Uttrakhand, India.
[2]Additional Professor, Department of Physiology, All India Institute of Medical Sciences, Rishikesh, Uttrakhand, India.
[3]Professor, Department of Physiology, All India Institute of Medical Sciences, Rishikesh, Uttrakhand, India.

***Corresponding Author: Dr. Prashant Kumar Saini**
Junior Resident, Department of Physiology, All India Institute of Medical Sciences, Rishikesh, Uttrakhand, India.

Article Received on 04/09/2023 **Article Revised on 25/09/2023** **Article Accepted on 15/10/2023**

ABSTRACT

Brain structures involved in brain-heart interactions comprise two primary areas: the central autonomic network, responsible for autonomic control (descending interactions), and the default mode network, which participates in the neural monitoring of cardiac activity (ascending interactions). Peripheral cardiovascular responses to standard physiological stimuli using multimodal recordings (ECG, Blood pressure) have been standardized and are available widely in the literature. The physiological stimuli most commonly used are a postural challenge, cold pressor stimulation, isometric exercise test, Valsalva Maneuver, etc. A central autonomic network (CAN) of interconnected brain structures regulates autonomic outflow to the heart. A lower heart rate variability (HRV) is associated with a cardiovascular disease and mortality risk; a high HRV value indicates good health. Higher HRV is associated with stronger vagus nerve function, lower chronic stress levels, better overall health, and improved cognition. This review discussed a more in-depth anatomy and physiological understanding of the connections between brain functions and related autonomic cardiac dynamics.

KEYWORDS: Autonomic cardiac dynamics**,** Autonomic network**,** Heart rate variability, Peripheral nervous system.

INTRODUCTION

Brain structures involved in brain-heart interactions comprise two primary areas: the central autonomic network, responsible for autonomic control (descending interactions), and the default mode network, which participates in the neural monitoring of cardiac activity (ascending interactions).[1] The pathways for bidirectional communication include discrete cortical centers, which respond to active commands or passive stimuli and act mainly in sympathetic or parasympathetic branches.[2] Since the heart and the brain are modulated by afferent and efferent signals and operate in unison, their simultaneous analysis will broaden our understanding of how these systems interact and govern our stress response.[3, 4] Peripheral cardiovascular responses to standard physiological stimuli using multimodal recordings (ECG, Blood pressure) have been standardized and are available widely in the literature. Such standard tests clubbed together as a standard battery (e.g., Ewing's battery of autonomic function tests) can be administered solely or as a whole battery to normal healthy populations or in various disease conditions. The physiological stimuli most commonly used are a postural challenge, cold pressor stimulation, isometric exercise test, Valsalva Maneuver, etc.[5,6] The responses to physiological stimuli are most commonly evaluated indirectly in terms of changes in absolute values of blood pressure or heart rate. In contrast, direct indicators of autonomic function, such as neural control of vessel diameter and resistance (e.g., autonomic control of systemic arterial pressure), are difficult to obtain.[6] Using time and frequency domain analysis of successive RR intervals in ECG, heart rate variability (HRV) analysis has become a promising non-invasive method for assessing autonomic tone in healthy and unwell persons. Systematic reviews and meta-analyses have shown that HRV analysis can be used to estimate mortality risk in myocardial infarction and for risk prediction of cardiac autonomic neuropathy (CAN) in diabetic mellitus patients. Regarding research, HRV may also be considered a surrogate parameter of the bilateral brain and cardiovascular system interaction. However, there is scarce information in the literature that suggests that abnormal brain–heart connections influence autonomic dysautonomia.[7-11] Given the clinical

importance of the brain-heart connection in many diseases, this implies that simple and reliable cardiovascular markers of sympathetic tone and sympathetic-parasympathetic balance are needed to develop particular clinical uses of knowledge on heart-brain interactions. Such markers would be essential for detecting early signals of cardiovascular dysautonomia, which can be treated to prevent the emergence of hazardous paroxysmal or chronic autonomic hyperactivity. This situation emphasizes the need for a more in-depth anatomy and physiological understanding of the connections between brain functions and related autonomic cardiac dynamics.

METHODS FOR SEARCHING

We explored the literature related to cardiac dynamics, the autonomic nervous system, sympathetic-parasympathetic balance, autonomic functions, the central autonomic network, brain-heart connection, and assessment of autonomic function. We browsed Cochrane, PubMed, Scopus, Embase, and Google Scholar databases. Keywords used are (central autonomic network) (autonomic nervous system [MeSH Terms]) AND (sympathetic nervous system[MeSH Terms])) AND (parasympathetic nervous system [MeSH Terms])) OR (brain-heart connection) OR (arterial blood pressure[MeSH Terms])) OR (heart rate variability[MeSH Terms])) OR (Cholinergic)) OR (adrenergic nerve fibers)) OR (autonomic functions) OR (peripheral nervous system[MeSH Terms]) OR autonomic cardiac dynamics ([[MeSH Terms]).

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS) is a peripheral neural system that regulates involuntary physiologic functions such as respiration, digestion, heart rate, blood pressure, and sexual arousal. It is divided into three anatomical divisions: sympathetic, parasympathetic, and enteric. Afferent and efferent fibers transmit sensory information and motor responses to the central nervous system (CNS) via the peripheral nervous system (PNS) (parasympathetic and sympathetic divisions).[12, 13] The activation of the SNS causes an increase in general activity and attention: the "fight or flight" response. Blood pressure and heart rate rise, glycogenolysis occurs, gastrointestinal peristalsis ceases, and so on.[14] Almost every living tissue in the body is innervated by the SNS. The PNS promotes "rest and digest" functions such as reduced heart rate and blood pressure, restarted gastrointestinal peristalsis/digestion, and so on.[14,15] The PNS innervates only the brain, viscera, and external genitalia, leaving much of the musculoskeletal system and skin uninvolved, much smaller than the SNS.[16] The ENS controls the digestive activities of muscle contraction/relaxation, secretion/absorption, and blood flow via reflex pathways.[17] Acetylcholine (ACh) is the neurotransmitter both the SNS and the PNS's presynaptic neurons use. Postsynaptic sympathetic neurons normally create norepinephrine (NE) to act on target tissues, whereas postsynaptic parasympathetic neurons use ACh continuously.[14,18] Enteric neurons have been observed to utilize a variety of neurotransmitters, including ACh, nitrous oxide, and serotonin, to mention a few.[19]

CENTRAL AUTONOMIC NETWORK

A network of neural networks between cortical and brainstem areas regulates the peripheral autonomic nervous system's function. Our endocrinological, psychological, and pain sensations are all regulated by the central autonomic network (CAN).[20] The sleep-wake cycle, arterial blood pressure, breathing, and other physiological events influence the central autonomic network's activity. The central nervous system's primary neurotransmitters govern neuronal transmission in the CAN, including glutamate, GABA, monoamines, neuropeptides, and nitric oxide.[5-7] The telencephalic components of the CAN are the orbitofrontal cortex, insular cortex, anterior cingulate cortex, amygdala, and hypothalamus. These upper areas, directly and indirectly, interact with lower brainstem centers, regulating peripheral autonomic activity. The nucleus tractus solitaries (NTS) is the initial relay station of autonomic activity, generating upward projections to the cranial parasympathetic nuclei. It controls all cardiovascular, pulmonary, and gastrointestinal (GI) autonomic responses.[21] The RVLM provides the primary excitatory output for vasomotor tone, whereas the medullary raphe nuclei produce sympathetic output implicated in thermoregulation and emotional reactions.[5,6] Stimulation of the insula and other parts of the central autonomic network was used to define the rostral components of the CAN.[8] These areas are linked to the spread of seizures.[9]

Septal Region

This area is also known as the ventromedial forebrain. The septal area is linked to several brain regions and the CAN via the fornix. Tachycardia is a significant autonomic response generated by the Stimulation of this region.[22]

Anterior cingulate cortex

This section of the medial frontal lobe extends to the parahippocampal gyrus via the paper circuitry to form the mesolimbic lobe associated with autonomic responses.[7] In rat models, Stimulation causes chest pain, low blood pressure, and micturition.[10]

The Hippocampal Complex

The subiculum, dentate gyrus, and hippocampus comprise this part of the medial temporal lobe. The amygdala, hippocampus complex, and parahippocampal gyrus are all part of the medial temporal lobe. These mesial temporal lobe components are notably affected in temporal lobe epilepsy. This area is related to the cingulate cortex and the hypothalamus via the Papez circuit, and aberrant electrical activity in this area has been shown to affect autonomic function.

Amygdala

The amygdala initiates autonomic reactions necessary for emotional expression and has multiple connections to the hypothalamus. It is located in the anterior temporal area and connects with the brain on the temporal pole's medial side.[11]

The Insular Cortex

This deep cortical region includes the frontal, temporal and vlobes on both sides of the brain. When this area is stimulated, the heart rate, blood pressure, breathing rate, gastrointestinal activity, adrenal medulla epinephrine secretion, piloerection, and pupillary dilation all rise.[20] Data suggests that insular autonomic activity is lateralized, activating the right and left insulas and eliciting sympathetic and parasympathetic activity, respectively.[11, 23]

Cortex olfactory

The medial forebrain bundle connects the olfactory region to the hypothalamus, the brainstem solitary nucleus, and the reticular formation.[11] In reaction to stimulus, gastric contraction, salivation, and amorous desire all increase.[5, 20]

Hypothalamus

The hypothalamus integrates all cortical inputs to the brainstem's autonomic regulation systems, especially the cardiovascular and respiratory centers.[5,11] The anterior and posterior hypothalamus are associated with parasympathetic and sympathetic functioning, respectively. Because of its connections to the key autonomic centers, the hypothalamic paraventricular nucleus generally impacts the autonomic nervous system.[24] The many modular regions of the cerebral cortex perform a supervisory role in autonomic control in the central autonomic network (CAN). These structures can induce various autonomic symptoms because of their vast connectivity.[25] **Fig. 1**

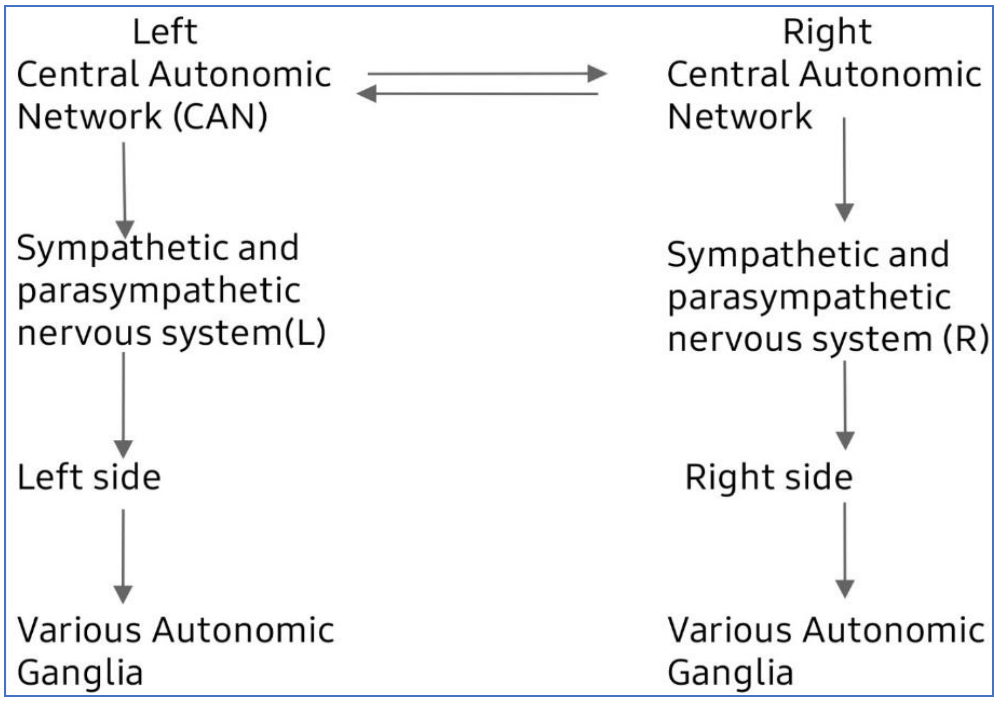

Figure -1: The intricate connections between the two cerebral hemispheres' CANs are shown schematically, as well as how the peripheral autonomic nervous system is specifically organized into sympathetic and parasympathetic branches that stay lateralized on either side.

Sympathetic neurons contain cell bodies in the spinal cord's intermediolateral columns, also known as the lateral horns. Presynaptic fibers exit the spinal cord via anterior roots and travel to the anterior rami of the T1-L2 spinal nerves, connecting to the sympathetic trunks via white rami communicantes. The fibers can then ascend or descend the sympathetic trunk to a superior or inferior paravertebral ganglion, or they can pass down the root continue through an abdominopelvic splanchnic nerve to a prevertebral ganglia.[26] Because of the sympathetic ganglia's central placement, presynaptic fibers are shorter than postsynaptic counterparts.[12,13] A preganglionic fiber or neuron is an axon from the central nervous system that projects to a sympathetic ganglion, symbolizing the output from the CNS to the ganglion. Preganglionic sympathetic fibers are generally short and myelinated because the sympathetic ganglia are close to the vertebral column. A postganglionic fiber—the axon generated by a ganglionic neuron that extends to the target effector—represents the ganglionic neuron's output that directly influences the organ. Postganglionic sympathetic fibers are longer than preganglionic fibers because of the

higher distance between the ganglion and the target effector.[12, 13] Pre- and postganglionic neurons synapse in paravertebral ganglia, which appear as nodules throughout the sympathetic trunk close to the spinal column. There are cervical, thoracic, four lumbar, and sacral ganglia, though the numbers vary depending on the individual.[27] The only ones with names are the superior, intermediate, and inferior cervical ganglia. The union of the inferior cervical ganglion with the first thoracic ganglion forms the stellate ganglion.[12, 13] As previously established, the SNS allows the body to deal with stressors by activating the "fight-or-flight" response. This response is principally responsible for blood vessel regulation. Vessels are tonically innervated, and an increase in sympathetic impulses usually results in vasoconstriction, the inverse of vasodilation. The exceptions are coronary arteries and vessels, which supply the skeletal muscles, and external genitalia, which have the opposite effect.[13] The equilibrium of alpha and beta receptor activation mediates this paradoxical effect. Beta-receptor activation enhances coronary artery dilatation in a normal state, but this effect is diminished by alpha-receptor-mediated vasoconstriction. In pathologic conditions like coronary artery disease, alpha-receptor activity increases while beta-activity decreases. As a result of sympathetic activation, the coronary arteries may contract.[28, 29] Sympathetic activation raises heart rate and contractile force but also increases metabolic demand, which harms cardiac function in people who are already sick.[30] Even in non-stressful conditions, the SNS is continually functioning. The SNS is active during the regular breathing cycle, in addition to the previously stated tonic activation of blood vessels. Sympathetic activation works in tandem with the PNS to widen the airways during inspiration, allowing for an optimal influx of air.[13, 31]Fig. 2

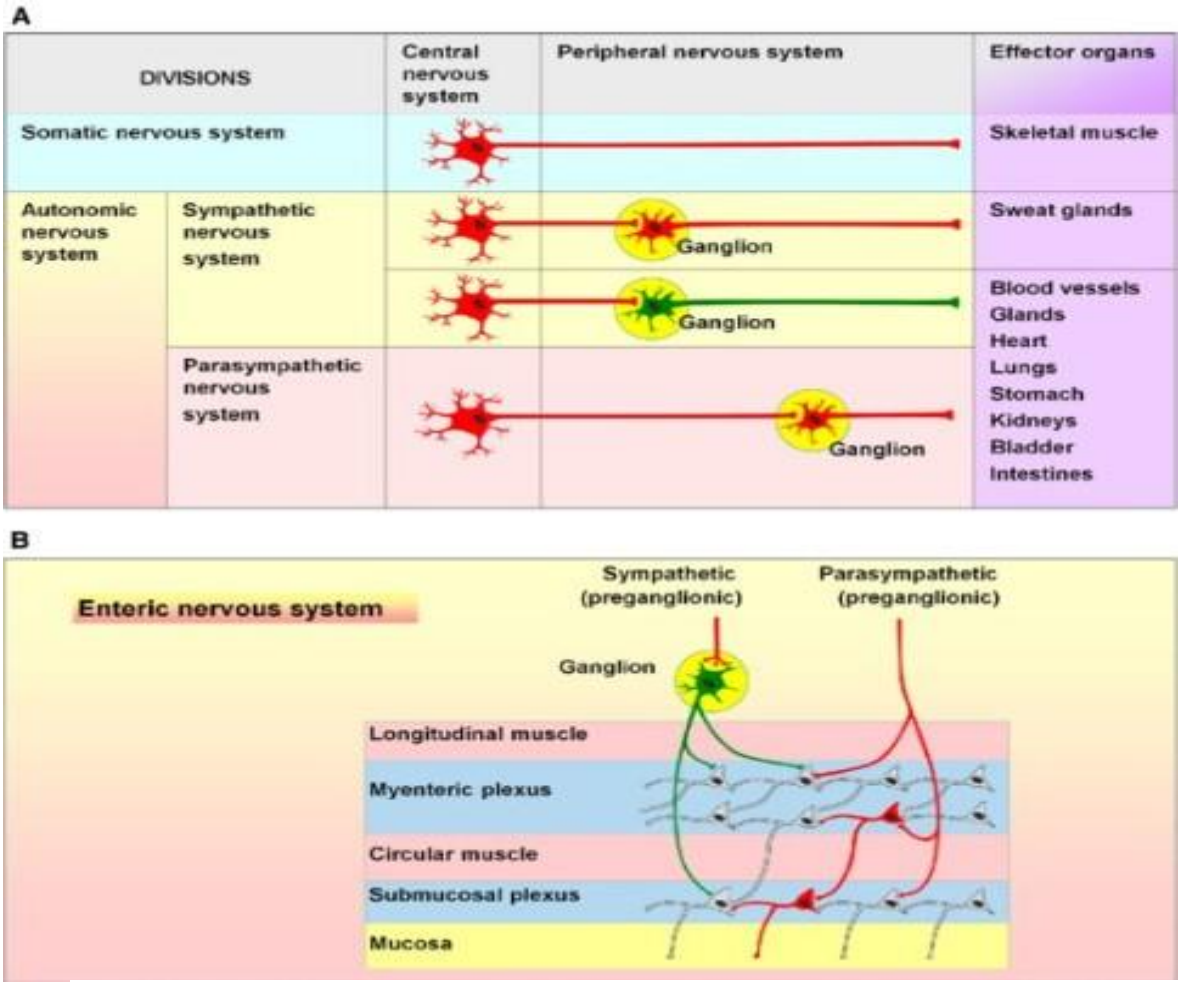

Figure 2: A diagram of somatic and autonomic divisions of the peripheral nervous system. (b) A simplified diagram of the enteric nervous system. Interaction at the effector junction of the autonomic nerve. At nerve effector junctions, cholinergic and adrenergic neurons coexist. Following neurotransmitter release, a particular neuron is reciprocally inhibited through a specific pre and post-junctional neurotransmitter receptor. Antagonism in the peripheral autonomic nerve system is often based on this. (Taken from : Malomouzh A, Ilyin V, Nikolsky E. 2019)[32]

Parasympathetic fibers leave the CNS through the cranial nerves -III, IX, VII, and X, as well as the S2-4 nerve roots. The parasympathetic ganglia are divided into four pairs and are all found in the head. CN III innervates the

iris and ciliary muscles of the eye via the ciliary ganglion. The pterygopalatine ganglion innervates the lacrimal, nasal, palatine, and pharyngeal glands and the sublingual and submandibular glands via the submandibular ganglion. The otic ganglion innervates the parotid glands via cranial nerves- IX.[33] Every presynaptic parasympathetic fiber synapses in a ganglion near or on the target tissue's wall, resulting in significantly longer presynaptic fibers than postsynaptic fibers.[13] The introduction states that the vagus nerve controls the "rest and digest" processes. The vagus nerve induces heart relaxation in a variety of ways. It reduces contractility in the atria but not in the ventricles. It mostly slows conduction through the atrioventricular node. Carotid sinus massage works by this method to inhibit reentry in Wolff-Parkinson-White syndrome. The PNS's other important function is digesting. Parasympathetic fibers to the head increase salivation, while those to the ENS increase peristaltic and secretory activity.[33, 34] The vagus nerve also affects the respiratory cycle. Parasympathetic nerves fire during expiration in a nonpathological state, constricting and constricting airways to prevent collapse. This function has linked the PNS to the onset of postoperative acute respiratory distress syndrome.[13, 31] Because of its broad breadth, the vagus nerve has been described as an early warning system for foreign invaders and for monitoring the body's recovery. Approximately 80% of vagal fibers are sensory and innervate almost all important organs. Interleukin-1 receptors have been discovered in parasympathetic ganglia, a crucial cytokine in the inflammatory immune response.[35] This, in the meantime, activates the hypothalamic-pituitary-adrenal axis, resulting in the release of glucocorticoids and NE.[13] In studies, viral activity inhibition via vagotomy and cholinergic inhibitors has been linked to considerably reduced, if not eliminated, allergy, asthmatic, and inflammatory reactions.[36]

The sympathetic and parasympathetic cardiac mechanisms are antagonistic in that they have opposing effects on myocardial cAMP levels and, as a result, on HP, atrioventricular conduction time, ventricular contractility, and relaxation rate. Evidence that prolonged parasympathetic activity reduces sympathetic noradrenaline release supports an inhibitory presynaptic connection.[37] The autonomic control of mean heart rate values (i.e., 1/HP) exhibits increased nonlinear antagonism, with even high levels of sympathetic activity having little impact when parasympathetic activity is equally high.[38] This nonlinear interaction is significantly less noticeable regarding atrioventricular conduction time and even mean HP values, which are readily explained by a linear combination of sympathetic and parasympathetic effects.[38, 39] In terms of autonomic modulation, the activity of each autonomic branch boosts the changes in heart rate caused by the modulation of the other unit.[40] This synergistic interaction implies that the high-frequency fluctuations in heart rate characterizing respiratory sinus arrhythmia are exacerbated by sympathetic activity and are not caused just by parasympathetic modulation, as might have been expected based on the frequency response properties discussed previously.[40] However, examination of HP variations revealed that beta-adrenergic inhibition promotes respiratory sinus arrhythmia in humans.[41] These disparities highlight that the effects of interactions in parasympathetic and sympathetic activities on cardiac function are complex and still poorly understood and that inequalities between analyses based on HP and analyses based on heart rate may contribute to the variability in reported results.

CENTRAL AUTONOMIC NETWORK AND CARDIOVASCULAR FUNCTIONA central autonomic network (CAN) of interconnected brain structures regulates autonomic outflow to the heart, including the medial prefrontal cortex (MPFC) and insular cortex It also included the amygdala, the bed nucleus of the stria terminalis (BNST), dorsomedial hypothalamic (DMH) nucleus, the paraventricular nucleus (PVN), the periaqueductal, and the lateral region of the hypothalamus.[42] The medial prefrontal cortex, includes the anterior cingulate cortex and the prelimbic and infralimbic areas, is engaged in cognitive and visceromotor activities, making it potentially important for psychosomatic medicine.[43] The insula is a viscerosensory and visceromotor area important in physiological and pathological cardiovascular regulation.[44,45] The right (non-dominant) anterior insular cortex in humans is important in forming a mental representation of one's physical situation, which underpins basic emotional experiences.[46] The amygdala predominantly involves negative emotion-related information processing, whereas happy emotions tend to lower amygdala activation.[47] The insular cortex, amygdala's central nucleus, and BNST create a corticostriatal-pallidal circuit that processes emotional information with autonomic responses and projects to the hypothalamic behavior control column.[42,48] The PVN is the master controller of the autonomic nerve system, giving specialized innervation to all autonomic relay centers[42] and integrating neuroendocrine, homeostatic, and stress responses with the DMH.[49] The PAG controls autonomic responses to physical and psychological stimuli. The NTS medullary nucleus and the pontine parabrachial and Kölliker-Fuse nuclei are all reciprocally linked and transfer visceral afferent information to other CAN structures.[51] The CAN in the medulla contains the NAmb and DMNX, the rostral ventrolateral medulla (RVLM) and caudal sections, and the rostral ventromedial medulla (RVMM), which includes the midline medullary raphe and the parapyramidal area.[51]

The cerebral cortex and other central autonomic network (CAN) areas regulate cardiovascular autonomic function.[52, 53] Reciprocal bilateral connections between the upper and lower centers of the central autonomic network are responsible for such an integration of this control. A lower HRV is associated with a higher

mortality risk and cardiovascular disease; a high HRV value indicates good health. Higher HRV is associated with stronger vagus nerve function, lower chronic stress levels, better overall health, and improved cognition. Likewise, the baroreceptor reflex, which regulates the amount of sympathetic and parasympathetic input to the cardiovascular system to maintain systemic blood pressure, forms the basis for assessing baroreflex sensitivity (BRS). Tests like paced breathing, Valsalva Maneuver, head-up tilt, and head-down tilt have been used as a physiological challenge to induce changes in ABP and to study cerebrovascular hemodynamic response.[6] Several researchers have claimed that neuronal activation in CAN like anterior cingulate cortex (ACC), insular cortex (IC), lateral prefrontal cortex (LPFC), medial prefrontal cortex (MPFC), dentate nucleus (DN), rostral ventrolateral medulla (RVLM), fastigial nucleus (FN), caudal ventrolateral medulla (CVLM), show a high correlation with beat to beat changes in heart rate.[4,20, 28,53] Mostly, these studies are performed using functional magnetic resonance imaging (fMRI) scans during various autonomic challenges like lower body negative pressure (LBNP), Head upright tilt table test, Valsalva Maneuver, and paced breathing. This neuronal activation is marked by an increase in [O2Hb] and a decrease in [HHb] concentration.[9] However, the relation between peripheral cardiovascular autonomic function tests has not been studied mechanistically in healthy human subjects, along with assessment and correlation (phase coherence) of cerebrovascular reactivity using functional near-infrared spectroscopy (fNIRS). Table 1.

Table 1 Fundamental comparison between peripheral and cerebrovascular circulation.

Peripheral circulation	Cerebral circulation
Large and small vessels act as conduits. Small vessels, specifically arterioles, act as resistance vessels.	The large and small cerebral arteries act as resistance and conduit vessels and can dilate and contract to regulate CBF.
Blood flow in peripheral circulation depends on Arterial Blood Pressure and venous pressure.	Cerebral perfusion depends on both Arterial Blood Pressure and Intra-Cranial Pressure.
Vasoconstriction of the arteries and veins and a decrease in blood flow are caused by sympathetic Stimulation of the peripheral circulation.	Other vasoconstrictive substances, blood vessel location, and the receptors' density and distribution affect cerebral circulation's reactivity to sympathetic Stimulation.
	According to the stimuli (intrinsic or systemic variables) and the blood vessel's location, increased cerebral sympathetic activity causes constriction or dilatation.
Postganglionic sympathetic nerves innervate the peripheral blood vessels' arteries, arterioles, and veins. The peripheral vasculature lacks parasympathetic innervation and is only regulated by the sympathetic nervous system.	Both sympathetic and parasympathetic nerve fibers densely innervate the cerebral circulation.
Small arteries and arterioles are composed of more smooth muscle cells than larger arteries.	Large intra- and extracranial arteries have multiple layers of smooth muscle cells, which are reduced to a single layer in cerebral arterioles.

CONCLUSION

A central autonomic network (CAN) of interconnected brain structures regulates autonomic outflow to the heart. A lower HRV is associated with a higher mortality risk and cardiovascular disease; a high HRV value indicates good health. Higher HRV is associated with stronger vagus nerve function, lower chronic stress levels, better overall health, and improved cognition. However, the relation between peripheral cardiovascular autonomic function tests has not been studied mechanistically in healthy human subjects, along with the assessment and correlation of cerebrovascular reactivity using fNIRS. From the standpoint of the clinician, electrocardiogram-based HRV holds promise as an appealingly simple tool for detecting autonomic impairments and forecasting the future course of some neurological disorders through the assessment of brain-heart connections. Unfortunately, we are still far from meeting this critical unmet need. HRV analysis should be undertaken in clinical situations to assess mortality risk in patients following myocardial infarction and to detect early indications of cardiac autonomic neuropathy in diabetic patients.

REFERENCES

1. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front Psychol, 2014 Sep 30; 5: 1040.
2. Rim D, Henderson LA, Macefield VG. Brain and cardiovascular-related changes are associated with aging, hypertension, and atrial fibrillation. Clin Aut Res, 2022; Dec 32(6): 409–22.
3. Dampney RA. Central neural control of the cardiovascular system: current perspectives. Adv Physiol Educ, 2016; Sep; 40(3): 283–96.
4. Forstenpointner J, Maallo AMS, Elman I, Holmes S, Freeman R, Baron R, et al. The solitary nucleus connectivity to key autonomic regions in humans. Eur J Neurosci, 2022 Jul; 56(2): 3938–66.
5. Gmitrov J. Baroreceptor stimulation enhanced nitric

oxide vasodilator responsiveness, a new aspect of baroreflex physiology. Microvasc Res, 2015 Mar; 98: 139-44.
6. Joyner MJ. Preclinical and clinical evaluation of autonomic function in humans. J Physiol, 2016 Jul 15; 594(14): 4009–13.
7. Riganello F, Prada V, Soddu A, Di Perri C, Sannita WG. Circadian rhythms and measures of CNS/autonomic interaction. Int J Environ Res Public Health, 2019 Jul 2; 16(13): 2336.
8. Tameemm A, Krovvidi H. Cerebral physiology. Vol. 13, Continuing Education in Anaesthesia, Critical Care and Pain, 2013; 113–118 p.
9. Villien M, Wey HY, Mandeville JB, Catana C, Polimeni JR, Sander CY, et al. Dynamic functional imaging of brain glucose utilization using fPET-FDG. Neuroimage, 2014; 100: 192–9.
10. Ainslie PN, Brassard P. Why is the neural control of cerebral autoregulation so controversial. F1000Prime Rep, 2014 Mar; 6: 5–10.
11. Mtui E, Gruener G, Dockery P. Fitzgerald's Clinical Neuroanatomy and Neuroscience E-Book. Elsevier Health Sciences, 2020 Aug 4.e.
12. Sternini C. Organization of the peripheral nervous system: autonomic and sensory ganglia. J Investig Dermatol Symp Proc, 1997 Aug; 2(1): 1-7.
13. Karemaker JM. An introduction into autonomic nervous function. Physiol Meas, 2017 May; 38(5): R89-R118.
14. Koopman FA, Stoof SP, Straub RH, Van Maanen MA, Vervoordeldonk MJ, Tak PP. Restoring the balance of the autonomic nervous system as an innovative approach to the treatment of rheumatoid arthritis. Mol Med, 2011 Sep-Oct; 17(9-10): 937-48.
15. Kenney MJ, Ganta CK. Autonomic nervous system and immune system interactions. Compr Physiol, 2014 Jul; 4(3): 1177-200.
16. Scott GD, Fryer AD. Role of parasympathetic nerves and muscarinic receptors in allergy and asthma. Chem Immunol Allergy, 2012; 98: 48-69
17. Lake JI, Heuckeroth RO. Enteric nervous system development: migration, differentiation, and disease. Am J Physiol Gastrointest Liver Physiol, 2013 Jul 01; 305(1): G1-24.
18. Sternini C. Organization of the peripheral nervous system: autonomic and sensory ganglia. J Investig Dermatol Symp Proc, 1997 Aug; 2(1): 1-7.
19. McConalogue K, Furness JB. Gastrointestinal neurotransmitters. Baillieres Clin Endocrinol Metab, 1994 Jan; 8(1): 51-76.
20. Li YW, Li W, Wang ST, Gong YN, Dou BM, Lyu ZX, Ulloa L, Wang SJ, Xu ZF, Guo Y. The autonomic nervous system: A potential link to the efficacy of acupuncture. Front Neurosci, 2022 Dec 8; 16: 1038945.
21. Jean A. Le noyau du faisceau solitaire: aspects neuroanatomiques, neurochimiques et fonctionnels [The nucleus tractus solitarius: neuroanatomic, neurochemical and functional aspects]. Arch Int Physiol Biochim Biophys, 1991 Sep; 99(5): A3-52.
22. Butler T, Blackmon K, Zaborszky L, Wang X, DuBois J, Carlson C, Barr WB, French J, Devinsky O, Kuzniecky R, Halgren E, Thesen T. Volume of the human septal forebrain region is a predictor of source memory accuracy. J Int Neuropsychol Soc, 2012 Jan; 18(1): 157-61.
23. Penfield W, Rasmussen T. The cerebral cortex of man; a clinical study of localization of function, 1950;
24. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci, 2006; 8(4): 383-95.
25. Ruffle JK, Hyare H, Howard MA, Farmer AD, Apkarian AV, Williams SCR, Aziz Q, Nachev P. The autonomic brain: Multi-dimensional generative hierarchical modelling of the autonomic connectome. Cortex, 2021 Oct; 143: 164-179.
26. Gardner ED, Bunge RP. Chapter 2 - Gross Anatomy of the Peripheral Nervous System. In: Dyck PJ, Thomas PK, editors. Peripheral Neuropathy (Fourth Edition) [Internet]. Philadelphia: W.B. Saunders; 2005 [cited 2023 Aug 24]. p. 11–33. Available from: https://www.sciencedirect.com/science/article/pii/B9780721694917500053.
27. Thayer JF, Sternberg EM. Neural aspects of immunomodulation: focus on the vagus nerve. Brain Behav Immun, 2010 Nov; 24(8): 1223-8.
28. Zamrini EY, Meador KJ, Loring DW, Nichols FT, Lee GP, Figueroa RE, et al. Unilateral cerebral inactivation produces differential left/right heart rate responses. Neurology, 1990 Sep 1; 40(9): 1408.
29. Heusch G, Thämer V. [Significance of the sympathetic nervous system for the coronary circulation]. Z Kardiol, 1984 Sep; 73(9): 543-51.
30. Vargas Pelaez AF, Gao Z, Ahmad TA, Leuenberger UA, Proctor DN, Maman SR, Muller MD. Effect of adrenergic agonists on coronary blood flow: a laboratory study in healthy volunteers. Physiol Rep, 2016 May; 4(10)
31. Chen IC, Kuo J, Ko WJ, Shih HC, Kuo CD. Increased flow resistance and decreased flow rate in patients with acute respiratory distress syndrome: The role of autonomic nervous modulation. J Chin Med Assoc, 2016 Jan; 79(1): 17-24.
32. Malomouzh A, Ilyin V, Nikolsky E. Components of the GABAergic signaling in the peripheral cholinergic synapses of vertebrates: a review. Amino Acids, 2019 Aug; 51(8): 1093-1102.
33. Siéssere S, Vitti M, Sousa LG, Semprini M, Iyomasa MM, Regalo SC. Anatomic variation of cranial parasympathetic ganglia. Braz Oral Res, 2008 Apr-Jun; 22(2): 101-5.
34. Wood JD. Application of classification schemes to the enteric nervous system. J Auton Nerv Syst, 1994 Jun; 48(1): 17-29.
35. Thayer JF, Sternberg EM. Neural aspects of immunomodulation: focus on the vagus nerve. Brain Behav Immun, 2010 Nov; 24(8): 1223-8.

36. Scott GD, Fryer AD. Role of parasympathetic nerves and muscarinic receptors in allergy and asthma. Chem Immunol Allergy, 2012; 98: 48-69.
37. Levy MN, Blattberg B. Effect of vagal stimulation on the overflow of norepinephrine into the coronary sinus during cardiac sympathetic nerve stimulation in the dog. Circ. Res, 1976; 38: 81–84.
38. Levy MN, Zieske H. Autonomic control of cardiac pacemaker activity and atrioventricular transmission. J. Appl. Physiol, 1969; 27: 465–470.
39. Ursino M. Interaction between carotid baroregulation and the pulsating heart: a mathematical model. Am. J. Physiol. Heart Circ. Physiol, 1998; 275: H1733–H1747.
40. Sunagawa K, Kawada T, Nakahara T. Dynamic nonlinear vago-sympathetic interaction in regulating heart rate. Heart Vessels, 1998; 13: 157–174.
41. Taylor JA, Myers CW, Halliwill JR, Seidel H, Eckberg DL. Sympathetic restraint of respiratory sinus arrhythmia: implications for vagal-cardiac tone assessment in humans. Am. J. Physiol. Heart Circ. Physiol, 2001; 280: H2804–H2814.
42. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clinic Proc. Mayo Clinic, 1993; 68: 988–1001.
43. Lane RD. Neural substrates of implicit and explicit emotional processes: a unifying framework for psychosomatic medicine. Psychosom. Med, 2008; 70: 214–231.
44. Verberne AJ, Owens NC. Cortical modulation of the cardiovascular system. Prog. Neurobiol, 1998; 54: 149–168.
45. Nagai M, Hoshide S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. J. Am. Soc. Hypertens, 2010; 4: 174–182.
46. Craig DA. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev. Neurosci, 2002; 3: 655–666.
47. Burgdorf J, Panksepp J. The neurobiology of positive emotions. Neurosci. Biobehav. Rev, 2006; 30: 173–187.
48. Swanson LW. Cerebral hemisphere regulation of motivated behavior. Brain Res, 2000; 886: 113–164.
49. Thompson RH, Swanson LW. Structural characterization of a hypothalamic visceromotor pattern generator network. Brain Res. Rev, 2003; 41: 153–202.
50. Bandler R, Keay KA, Floyd N, Price J. Central circuits mediating patterned autonomic activity during active vs passive emotional coping. Brain Res. Bull, 2000; 53: 95–104.
51. Dampney RAL.Functional organization of central pathways regulating the cardiovascular system. Physiol. Rev. 994 ; 74, 323–364.
52. Talman WT, Kelkar P. Neural control of the heart. Central and peripheral. Neurol Clin, 1993 May 1; 11(2): 239-56.
53. McBryde FD, Malpas SC, Paton JFR. Intracranial mechanisms for preserving brain blood flow in health and disease. Acta Physiol, 2017 Jan; 219(1): 274–87.