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Indian Journal of Physiology and Pharmacology

Review Article

The vagus nerve in psychiatry: From theories to therapeutic neurostimulation in neuropsychiatric disorders

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Received: 01 September 2022
Accepted: 11 August 2023
EPub Ahead of Print: 30 September 2023
Published: 10 October 2023

DOI:
10.25259/IJPP_401_2022

Quick Response Code:

ABSTRACT

The vagus nerve (VN) plays an important role in the modulation of the autonomic nervous system, inflammatory system, and interoception, therefore connecting the cardiovascular and gastrointestinal systems to the central nervous system. Dysregulation of the VN is implicated in several psychiatric disorders. The recent availability of safe and non-invasive transcutaneous VN stimulation (tVNS) techniques opens new opportunities to evaluate the role of the VN in psychiatric disorders. We briefly review the basic anatomy and physiology of the VN, extensively discuss various theories linking VN dysfunction to health and illness, give details of the probable neurochemical underpinnings of VN activity, delineate its dysfunction in psychiatric disorders and put forward the current state and future directions of VNS, specifically focusing on tVNS.

Keywords: Neurovisceral integration model, Polyvagal theory, Transcutaneous vagus nerve stimulation, Vagus nerve, Vagus nerve stimulation

INTRODUCTION

The vagus nerve (VN) (the 10th cranial nerve [CN]) is the longest and probably the most versatile CN in our body.[1] It may be the first to pick up physiological disturbances in the body through its afferent and efferent fibres and also the earliest to respond to the same. It affects the cardiovascular, respiratory, and gastrointestinal systems by innervating the visceral organs and regulating the autonomic nervous system (ANS). It regulates the inflammation cascade.[2,3] The VN is often implicated in psychiatric conditions due to its wide range of functions.

Vagus nerve stimulation (VNS) has been used for treatment-resistant epilepsy and depression, chronic pain syndromes, and headaches. The VN can be stimulated in the traditional invasive VNS (iVNS) method through surgery. Recently, non-invasive or minimally invasive techniques such as percutaneous and transcutaneous VNS (tVNS) are becoming popular. tVNS is usually either cervical VNS (cVNS) or trans-auricular VNS (ta-VNS).[4] Overall, tVNS provides a safe method to test the potential of VN neurostimulation as an investigative and therapeutic tool.[5] At this juncture, we should look at what the VN has to offer to enhance our understanding of general health, particularly psychiatric disorders. Therefore, we believe that this review is essential and timely to provide an overview of these recent advances. Here, we briefly note the anatomy and physiology of the VN, discuss various VN-related theories on human health and psychology,

and ways through which the VN may be related to psychiatric disorders. Finally, we briefly discuss the procedure of tVNS, its potential, and future directions.

BASIC ANATOMY AND PHYSIOLOGY

The VN has anatomically four nuclei of origin: the dorsal motor nuclei of the vagus (DMNV), the nucleus ambiguus (NA), the nucleus of the spinal tract of the trigeminal nerve (TN) and the nucleus of the solitary tract (NTS). These four nuclei have been classified as motor (NA), sensory (spinal tract of TN and NTS), and parasympathetic (DMNV) nuclei. The DMNV is paired, symmetrical, and predominantly made of parasympathetic preganglionic nuclei (80%). Its efferent fibres connect with the parabrachial nucleus, cerebellar nuclei, and cerebral cortex.[6-8] The fibres from NA mainly control motor movements of swallowing and speech. Some of its fibres innervate the heart and regulate the parasympathetic.[8-10] The spinal trigeminal nucleus contains afferent sensory fibres with cell bodies in the superior or jugular ganglion: The NTS forms general and special visceral afferent pathways (General visceral afferent [GVA] and special visceral afferent [SVA], respectively). The GVA component innervates the thorax, abdomen, and mucous membranes. The SVA component receives taste afferents.[8,10] These are summarised in [Table 1]. Theories that explain the functions of the VN often give prime importance to these various nuclei of origins, proposing that the fibres from a specific nucleus may function differently than those from another.

After arising from the medulla, the VN leaves the cranium through the jugular foramen. It gives the auricular branch of VN (ABVN).[8] This is the branch of the vagus that is targeted non-invasively through ta-VNS. The ABVN forms the rounded superior ganglion and cylindrical inferior ganglion (both sensory) at the jugular foramen. Here, it is also joined by the cranial root of the accessory spinal nerve. The VN remains in the carotid sheath in the neck thereafter, along with the internal jugular vein and the internal and common carotid arteries. This is the target region of cVNS. From here, the right and left VNS have slightly different paths, which may have clinical applications. Laterality becomes important for safety and effectiveness. Animal studies show that right-sided stimulation has stronger effects on the heart, and therefore, left-sided VNS is preferred in humans. However, safety concerns like arrhythmia are not higher in the right-sided VNS.[4,5] The right side of the heart is also considered to contain more efferent vagal fibres, which can show differential effects of stimulation. Stimulating both sides may lead to a higher ('summation') effect as well. Again, these features have not been evaluated sufficiently.[11]

The right VN enters the thorax contributes to the pulmonary plexus and oesophageal plexus, and then, through the diaphragm reaches the gastrointestinal and renal system through the celiac, superior mesenteric, and renal plexuses. The left VN reaches the thorax and reaches the aortic arch, contributes to the pulmonary plexus and oesophageal plexus, and then reaches gastrointestinal organs through the oesophageal opening of the diaphragm. Throughout this course, the VN gives several branches such as meningeal, auricular, pharyngeal, carotid, superior laryngeal, recurrent laryngeal, cardiac, oesophageal, pulmonary, and gastrointestinal.[7,8,10]

Among the CNs (i.e., III, VII, IX, and X) that constitute a significant portion of the parasympathetic system, the VN makes the greatest contribution (i.e., about 75%). The VN is responsible for the regulation of cardiac relaxation, salivation and digestion, and the respiratory cycle.[12,13] Thus, the vagal influence on the parasympathetic function is one of the factors that underlie its neuromodulatory effects through VNS. Moreover, the specific type of nerve fibre composition influences the effects of stimulation. The VN contains A, B, and C, fibre groups. These have different speeds of conduction and activation thresholds. The afferent, large and myelinated

Table 1: Anatomical details.[6,8,10]

Nucleus	Situation	Main innervation	Functional category
Dorsal motor nuclei of the vagus	Dorsomedial caudal medulla oblongata, within the caudal rhomboid fossa	Structures (including involuntary muscles) in the head, neck, thorax, and abdomen	GVE
Nucleus ambiguus	Reticular formation of the medulla oblongata	Muscles of the soft palate, larynx and pharynx, heart	SVE
The nucleus of the spinal tract of the Trigeminal nerve	The lateral medulla of the brain stem	The external ear and acoustic meatus, tympanic membrane, and dura mater of the posterior cranial fossa	GSA
The nucleus of the solitary tract	Dorsomedial medulla oblongata, its cell bodies are situated in the inferior ganglion	Thorax, abdomen, and mucous membranes	GVA, SVA

GVE: General visceral efferent, SVE: Special visceral efferent, GSA: General somatic afferent, GVA: General visceral afferent, SVA: Special visceral afferent

A-fibres may be relevant for reducing seizures; whereas the efferent, myelinated B-fibres may be responsible for cardiac functioning; both type B and afferent, unmyelinated C-fibres are related to inflammation.[1,14,15] Stimulation of the B-type fibres may be essential to regulate the parasympathetic action of the VN.

However, the importance of the VN in the human body goes beyond the neuroanatomical and neurophysiological boundaries and fascinatingly extends to the social and evolutionary mechanisms. Below, we discuss several hypotheses relating to our general well-being and the pathological implications of VN dysfunction.

THEORIES RELATED TO VN AND HUMAN HEALTH

There are theories/concepts linking the VN, its effect on cardiovascular regulation, the ANS, cognition, and species evolution. These theories are important as they invariably link the VN to a diseased or dysfunctional state of the human body. Stress increases the heart rate, and therefore, a lower baseline heart rate is preferred. This lowering of the heart rate is predominantly brought about by the parasympathetic action, and therefore by the VN. This is measured through heart rate variability (HRV) and shows that a better HRV capacity is beneficial. However, lowering heart rate is also potentially fatal. Thus, the control of the cardiac rate at an optimum level is desired. The following theories propose and argue on how the VN nerve is regulated and, in turn, regulates the ANS, what may be the ideal range of cardiac and respiratory rates, the interaction between these parameters, and the mechanisms behind these. We briefly mention these below and also in [Table 2]:

The vagal paradox

While evaluating the roles of HRV and respiratory sinus arrhythmia (RSA) for health and stress vulnerability in infants, Porges observed that the VN could serve both as a protective agent (by RSA) and a dangerous agent (by inducing bradycardia). He termed this the 'Vagal Paradox', which challenged the prevailing idea of a 'single central vagal source'.[16,17] Porges argued that there must be at least two centres controlling the VN.

The Darwinian model

While proposing the evolutionary 'survival of the fittest' theory, Darwin considered that to survive, a species needed beyond the physiological fight-flight-freeze process. Those with consciously managed higher intelligence (including social and emotional) would probably have an advantage and survive. Therefore, 'survival of the fittest' was both a conscious and unconscious process. Darwin considered a secondary control centre other than the higher cognitive centre to be active. He considered the VN responsible for this bidirectional connection between the brain and the heart and called it the 'pneumogastric nerve'.[16,18-20]

The triune brain theory

A closely related theory (by MacLean) on the evolution of the brain, assumes that the human brain is the most advanced and is three-layered. It is built on the primitive layer of the reptilian brain focused mainly on the brainstem/basal ganglia, the limbic brain from mammals as the second layer, and the final layer of the neocortex focused more on language and abstraction.[21-23] The VN cuts across these three layers as it is relevant in the brainstem, limbic system, and neocortex. The limbic brain is responsible for the physiological reactions to stress but could be regulated by the higher neocortex. Therefore, mammals and especially humans possessing the biggest neocortex have the opportunity to master their physiological responses.

Central autonomic network (CAN)

From the above theories, it becomes clear that the VN and the brain have regulatory roles in physiological processes. Which areas of the human brain are responsible for this? CAN is proposed to be an internal regulation sub-system that includes mainly the insula, hypothalamus, amygdala, and NTS. This network may regulate interoception, pain, neuroendocrine and inflammatory functions. They also regulate preganglionic ANS. The CAN has a hierarchical setting with the insula and amygdala responsible for the higher-level control. Functioning of the CAN-related areas, therefore, become important in health and illness. Through CAN, brain-related disorders such as stroke, seizure, subarachnoid haemorrhage, and head injury can be connected to cardiorespiratory functions. It also has implications for sleep apnoea, hypo/hypertension, neuroleptic malignant syndrome, cardiac arrest, and anxiety disorders.[11,24,25]

The Polyvagal theory

Building on insights from the vagal paradox and phylogenetic concepts of the VN, Porges formulated the Polyvagal theory. As the name refers, it suggests that there is more than one vagal system. It proposes that the vertebrate ANS has evolved through three distinct phylogenetic stages. The most primitive of these acts through freezing in the face of danger and the second stage is mobilisation in the face of danger. Mammals are, further, evolved with myelinated fibres in the VN, and their response to danger is mediated through social communication. Anatomically, physiologically and phylogenetically, the NA and dorsal motor nuclei of vagus

Table 2: Connecting theories to clinical disorders and empirical uses.

Theory	Anatomical/ physiological focus	Cognitive/social/ psychological focus	Possible pathology/ outcome	Expected investigational findings	Expected psychiatric disorder
Darwinian	Bidirectionality of the VN	Emotional expression/ Recognition	Faulty facial and emotional recognition, poor social function	Reduced/abnormal facial emotion recognition, abnormal activation of left inferior frontal gyrus, lower HRV	Autism, Asperger's, depression, anxiety, misidentification syndrome
Polyvagal	Dual control of the VN	Social and emotional functioning	Abnormal detection, integration, and regulation by the VN	HRV, abnormal activation of the CAN-related areas, autonomic system biomarkers	Autism, depression, GAD, panic disorder, anxious personality traits
Triune Brain	Three-layered human brain	Emotional, facial, and vocal expression	The mismatch between three layers leads to faulty interpretation of external cues, 'maladaptive expressions of adaptive communicational states'[21]	Abnormal activation of the limbic systems, unpredictable heart rate, breathing rate, and blood pressure	Depression, anxiety
Neuro-visceral Integration	Cardiac vagal tone, central autonomic network, frontal-subcortical circuits	Emotional control, self-regulation, pull and push drives of motivation	Disintegration of autonomic, attentional, and affective domains	HRV, abnormal activation of the CAN-related areas, autonomic system biomarkers	GAD, depression, alexithymia, panic disorder, paranoid personality traits
Vagal tank	Cardiac vagal control, homeostatic processes	Self-control, conscious and effortful self-regulation	Poor efficiency of self-regulatory resources, their mobilisation, and utilisation	HRV, Prefrontal cortex activation	Depression, anxiety, eating disorders
Biological behavioural	Cardiac vagal tone, respiratory sinus arrhythmia	Social behaviour and communication	Mismatch of the behavioural and metabolic needs of the cardiorespiratory system	HRV, pulmonary function tests, autonomic system biomarkers	Depression, anxiety, autism
Resonance frequency	Cardiac-brain interactions	Affective, cognitive functions	Poor optimisation of HRV biofeedback, out-of-sync resonance frequency	HRV, autonomic system biomarkers	Mood disorders, panic disorder, GAD
Psychophysiological coherence	Slow-paced breathing	Emotional regulation	Physiological incoherence	HRV	Anxiety disorders, loss of general well-being

CAN: Central Autonomic Network, GAD: Generalised Anxiety Disorder, HRV: Hear Rate Variability, VN: Vagus nerve

(DMNV) are distinct vagal systems. While DMNV is primitive, NA is recently evolved and is implicated in the neural regulation of the heart and respiratory system. These also play a role in facial muscles, thus regulating social and emotional behaviour.[17,19,20] As in the previous theories, the cardiorespiratory regulation by the brain through the VN becomes important and the cardiac vagal tone is, therefore, the most important parameter for health.

The neurovisceral integration model

This model focuses on the link between cardiac vagal tone and emotional control by attention and self-regulation. Similar regions such as the orbitofrontal cortex, insula, amygdala, basal ganglia, and brainstem, act in both controls of the vagal tone and emotional expression and regulation. This similarity is not only anatomical but also functional. It was also observed that the resting HRV was related to prefrontal activity. A lower resting HRV was associated with hypofunction of the prefrontal cortex (PFC). Thus, a higher vagal tone relates to better executive, emotional and social functioning.[26-28]

The vagal tank theory

This builds on the neurovisceral integration model and the need for self-regulation of cognition and social behaviour.

It details three phases of cardiac vagal control: resting, reactivity, and recovery states. These states help in resource mobilisation (physiologically) and, therefore optimal self-control (socially and cognitively).[28,29]

The biological behavioural model

This model challenges the assumption in the Polyvagal theory that the cardiac vagal tone is specifically represented by the RSA.

The authors argue that for one RSA to be calculated, the heart rate should be 2 times it. After reanalysing previous data with corrective models such as Nyquist frequency and cardiac aliasing, they propose that cardiorespiratory coupling is more important for cardiac vagal control. This regulation of cardiac and respiratory systems is conducted by the VN. Therefore, the vagal tone works as an energy reserve and can be further used by the organism. The higher the vagal tone, the larger the reserve energy capacity and the better the animal's functioning.[28,30]

The resonance frequency model

The model reflects on the respiratory control of the VN. Through a resonance breathing pattern, the VN increases entrainment and relaying communications between the cardiorespiratory, ANS, and CNS. Improving the HRV by feedback loops may, thus, improve mood and cognition.[28,31,32]

The psychophysiological coherence model

This model builds on slow-paced breathing and physiological coherence, which is 'the degree of order, harmony, and stability in the various rhythmic activities within living systems over any given period'. Matching emotional regulation with slow-paced respiration would increase coherence and, therefore, improve well-being.[33-36]

The heart rhythm coherence model

This extends the psychophysiological coherence model to hypothesise that afferent baroreceptor signals may modulate CNS activity, which is then encoded in the short- and long-term memory of cardiac ganglia. The HRV patterns accumulate over a long time and may influence cognitive and emotional functions.[31,35]

The calming cycle theory

This handles the vagal paradox by introducing the mother of a neonate/foetus as the secondary control. It goes back to the intrauterine life of the foetus, and the coordination between the VNs of the foetus and the mother. Their ANS is thus co-ordinated even after birth, leading to attachment and thereafter social and emotional development. Healthy relationships, again, are denoted by a higher vagal tone.[16]

While these hypotheses are based on proposed mechanisms of VN action, which may at times seem more theoretical, biological evidence to back these claims has gradually been accumulated. The VN has been implicated in the regulation of various neurochemicals in our body, along with its overall function in the autonomic and inflammatory systems [Figure 1]. We briefly discuss these two aspects in the following sections.

THE VN AND NEUROCHEMICALS

Various neurochemicals such as dopamine, glutamate, serotonin, gamma-aminobutyric acid (GABA), norepinephrine (NE), oxytocin, and acetylcholine (Ach) are hypothesised in the etiopathogenesis of psychiatric disorders; interestingly, these neurotransmitters are intricately linked with VN. The major insights come from VNS in animal studies as well as a handful of *in vivo* human studies. Relevant details are given in [Table 3]. Dopamine and the VN interactions relate to mesolimbic and mesocortical dopaminergic pathways and, therefore, affect reward processing and hyperactivity.[37,38] Serotonin and the VN interaction may be of prime importance in regulating the gut-brain axis and, therefore, affect anxiety, mood, substance abuse, and psychotic disorders.[39-41] The VN has modulatory effects on the ANS through parasympathetic outflow on organs in the neck, thorax, abdomen, and pelvis. A lower parasympathetic tone is considered to be present in schizophrenia, mood, and anxiety disorders.[11] The VN seems to affect the ANS specifically through alpha-2 NE and Ach.[11] NE is also implicated in the gut-brain axis.[39,42] Moreover, the anti-epileptic effects of VNS may be NE-related.[43] Ach is of relevance for cognitive functions. Nicotinic Ach receptor alpha7 subunit (α7nAChRs) are specifically implicated in the neuro-immune axis.[11,44,45]

GABA plays a role in afferent information reaching the brain through the VN as well and may inhibit mechanoreception centrally.[46] GABA-ergic neurons are modulated through the VN during stress to relay information through the gut-brain axis (Hou *et al*.).[47] Some of the VN afferents projected to the NTS are glutamatergic. L-glutamate acts as a neurotransmitter in the afferent nerve groups of the VN.[48,49] These afferents regulate the baroreceptors and more extensively the cardiovascular system and the gut-brain axis.[11]

Oxytocin receptors are present in the DMNV and together with those in the hypothalamic paraventricular nucleus, interact through the ANS.[50] The VN may have inhibitory effects on peripherally administered oxytocin in drug (opioid) withdrawal.[51] The VN itself may contain opioid receptors, which have an inhibitory action on the cardiovascular system.[52] Opioid receptors play a role in nociception and endogenous pain control through vagal afferents.[53,54]

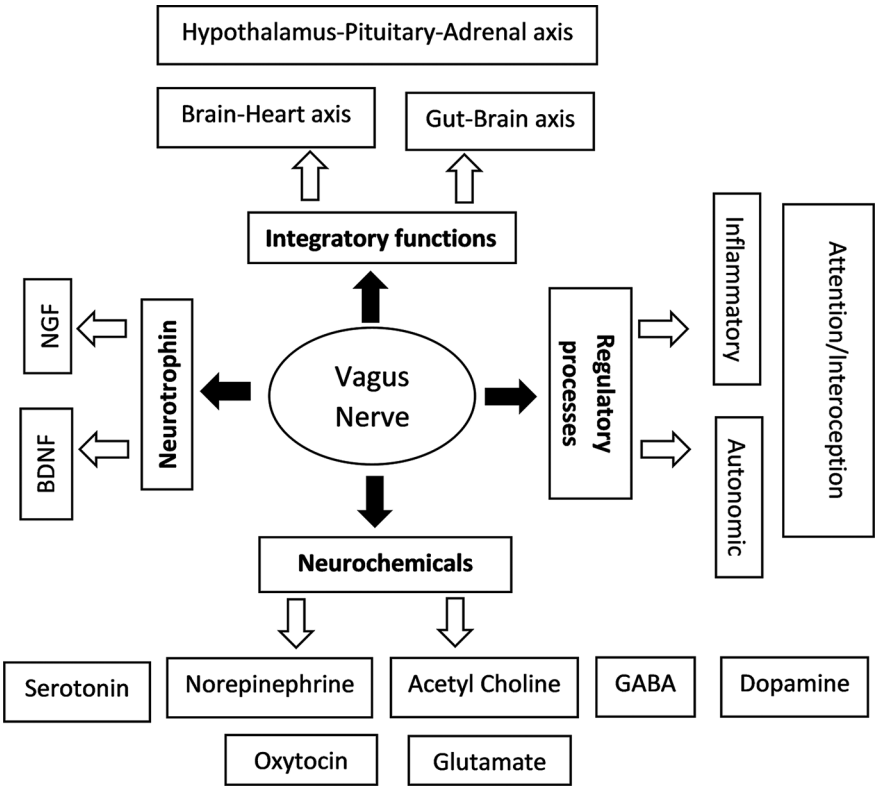

Figure 1: Impact of the vagus nerve on various neurophysiological processes. BDNF: Brain-derived neurotrophic factor, GABA: Gamma-aminobutyric acid, NGF: Nerve growth factor.

Table 3: Relationship between the VN and neurochemicals.

Neuro-transmitter	Species	Effects
Dopamine	Rats Pigs	Low-frequency VNS in rats inhibits dopaminergic actions, vagotomy may decrease dopamine in certain brain areas.[55]
	Human	Long-term VNS may lead to decreased dopamine neuronal activation in the ventral tegmental area and increased dopamine neuronal firing in extracellular dopamine levels in the PFC and nucleus accumbens.[56] Aberrant dopaminergic pathways in mesolimbic areas are seen to be modulated by VNS, and this, in turn, reverses the hyperactivity in the hippocampal region.[38] Changes in the structure of long-chain fatty acids and lipid unsaturation levels in the ventral tegmental area, motor cortex, and substantia nigra. Protein-related structural changes were also found in areas of dopaminergic pathways.[57] VNS increases dopamine levels in the striatum, mid-brain, amygdala, and hippocampus.[58] VNS increases invigoration which is directly related to dopamine status in the mesolimbic and mesocortical areas.[37]
Serotonin	Mice/Rats	SSRIs given to vagotomised mice do not show adequate antidepressant effects.[59]
	Cats	VNS fails to produce expected motor cortex plasticity when serotonin is available at inadequate levels.[40]
	Pigs	Increase the release of serotonin.[60] Serotonin receptors may increase in number.[58]
NE	Rats	Depletion of cortical NE decreases the expected cortical representation of limb movements.[40] Increased extracellular NE concentrations in the hippocampus and cortex, but this was stimulation parameters dependent.[61] Increased NE in PFC,[62] hippocampus,[63] locus coeruleus (model for anti-Parkinsonian effects).[64]
Oxytocin	Rats/mice	Increased levels of plasma oxytocin after afferent stimulation of the VN.[65] Suppression of feeding through afferent VN fibres by peripheral oxytocin.[66]

Ach: Acetylcholine, NE: Norepinephrine, SSRI: Selective serotonin reuptake inhibitor, VN: Vagus nerve, VNS: Vagus nerve stimulation, PFC: Prefrontal cortex

INFLAMMATION AND THE VN

The VN may serve as an important modulator of inflammation through the hypothalamus-pituitary-adrenal (HPA) axis, thoracolumbar sympathetic efferents, vago-sympathetic pathway, and central descending pathways. Especially, efferent cholinergic fibres of the VN influence the inflammatory responses through the inflammatory reflex.[3,11] The activation of the HPA axis by proinflammatory cytokines results in the release of glucocorticoids, or through the cholinergic anti-inflammatory pathway, by decreased cytokine production mediated by the central muscarinic receptors and α7nAchR or through reduction of TNF-α by splenic T-lymphocytes. Interaction between the vagus and the sympathetic nervous system through NTS may also have anti-inflammatory effects. Neurotrophins (NT) such as nerve growth factor and brain-derived neurotrophic factor (BDNF) may also play a part.[3] Vagotomy has been associated with reduced BDNF expression through messenger ribonucleic acid, specifically in the hippocampus in mice.[67] BDNF may play a regulatory role in the immune system; conversely, inflammation may reduce BDNF expression.[68] Further, VNS can induce plasticity in the hippocampal region, probably mediated by GABA and NT.[69]

The anti-inflammatory action of VNS has even been considered to reduce cytokine in viral infections.[70] The influence of VNS on cytokines is not restricted to inflammatory states. Even in healthy conditions, certain specifications of stimulus parameters may result in changes (even increases) in inflammatory markers.[71]

With such significant physiological functions attributed to the VN, its dysfunction certainly plays a major role in our ill health. Below we try to discuss the basic dysfunctions proposed to be involved in neuropsychiatric disease states and their implications.

VNS IN NEUROPSYCHIATRIC DISORDERS [FIGURE 2]

VN dysfunction is implicated in several neuropsychiatric disorders [Figure 2]. VNS has been used for treatment-resistant epilepsy. It significantly reduces seizure episodes in this population, increases the quality of life, and is relatively safe.[72] However, most iVNS has been used and, therefore, has surgery-related adverse effects. Increased cerebral blood flow in certain regions of the brain, modulation of NE and serotonin, 'quenching kindling of seizures', and anti-inflammatory effects have been hypothesised for its anti-epileptic effects.[73]

VNS is effective in treating pain syndromes, migraines, cluster headaches, trigeminal neuralgia, and fibromyalgia.[4] Chronic high level of stimulation reduces nociception. Here, the recruitment of unmyelinated C fibres and the intensity of the stimulation may be essential. Anti-nociception through the VNS also depends on the cognitive and affective components of the individual.[69] Functional connectivity between the amygdala, thalamus, hypothalamus, nucleus accumbens, basal ganglia, and insula regulate pain anticipation and experience, particularly from the viscera. Activation of these areas is seen with VNS and this may also be responsible for nociception.[74,75]

The impetus for using VNS in depression came when those with epilepsy who were treated with VNS reported better moods. VNS may influence neurochemical expression (NE, serotonin, and BDNF) in key brain regions and increase hippocampal neurogenesis. It may also affect the quality of functional connectivity along the cortical-limbic-thalamic-striatal neural circuit.[2] tVNS is found to significantly increase the functional connectivity between the nucleus accumbens, basal ganglia, and medial PFC. These areas are related to motivation and reward processing and thus, better functional connectivity may help to reduce depression.[76,77] In treatment-resistant depression, reduced blood flow to the limbic system and the frontal cortex was important for the therapeutic effects of iVNS.[69,78]

The VNS has been used to treat opioid withdrawal syndrome. The major benefit is obtained through modulation of the dysfunctional ANS in the withdrawal states.[53] Decreased VN activity may predict tobacco use, especially during stressful conditions.[79]

The VNS has been used in post-traumatic stress disorder by increasing the process of extinction of conditioned fearful stimuli. Its effects on the ANS may also play a part in fear conditioning and expressions.[80] Using a similar rationale, VNS has also been proposed for therapeutic benefits in anxiety disorders and obesessive-compulsive disorder (OCD).[81] Further, panic disorders are predominantly related to interoceptive disturbances which may be regulated by the VN. VNS also shows potential usefulness in eating disorders and schizophrenia, through its modulation of interoception, autonomic and inflammatory systems.[82,83] VNS is hypothesised to be beneficial in autism spectrum disorder by modulation of emotional social interaction, facial recognition, and facial expression processing.[84] It may also reduce temper tantrums and anger outbursts in neurodegenerative conditions and Prader–Willi syndrome.[85] Finally, VNS has been proposed to have beneficial effects on disorders of consciousness after brain injury. This is probably through the modulation of brain circuit networks such as the upper and lower brainstem, thalamus, and cortico-striatal-thalamic-cortical loop.[86,87]

The next important step is joining the bridges and understanding the gaps between the physiological and pathological interaction of VN functioning. To do so, we need to empirically test hypotheses and make scientific

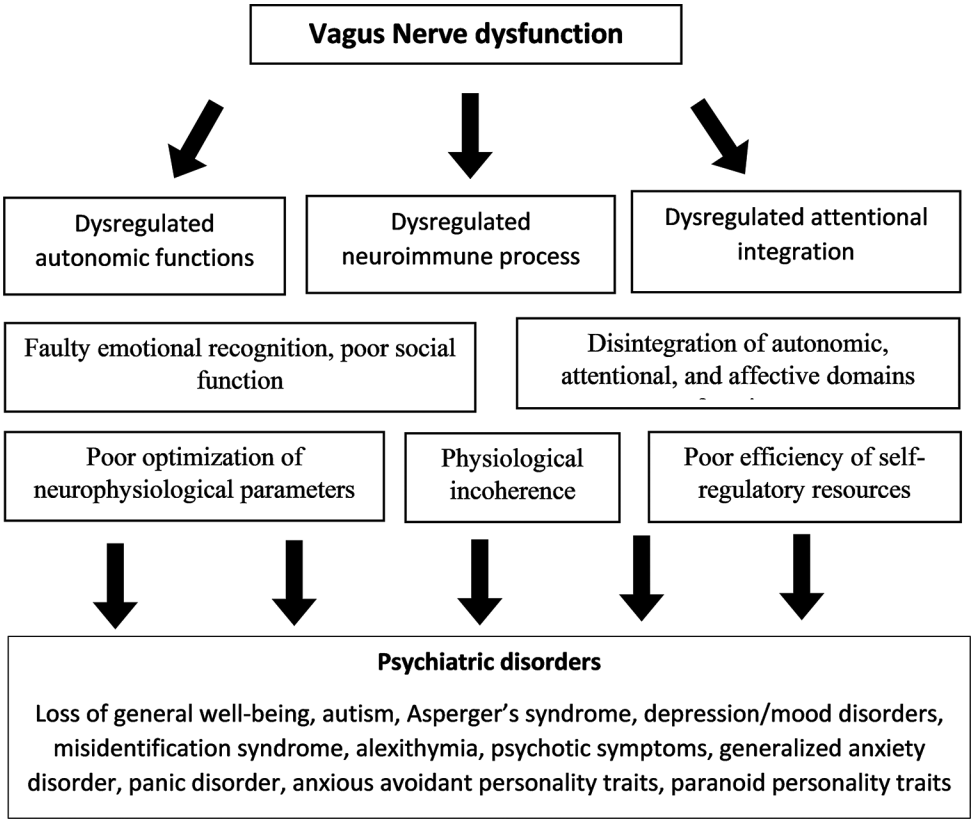

Figure 2: Vagus nerve dysfunction and probable effects on psychiatric disorders.

progress that can support integrated hypotheses and illness models – this is discussed in detail below.

TRANSLATING THEORIES TO EMPIRICAL TESTING

[Table 2] summarises the VN-related theories and links these with probable psychophysiological disturbances, ways to empirically test it, and possible psychiatric disorders due to malfunction. Parts of these hypotheses can be empirically tested by well-designed research. tVNS allows doing so; with direct ways to stimulate and therefore manipulate the VN, a causal relationship can be teased out. These experiments will lay the foundation of evidence for VN-related theories.[4,88,89] Supplemented with basic sciences related to animal experiment models, dysfunctions of the ANS and emotional/cognitive reactions can have a neurochemical scaffolding. This will translate to the current neurochemical-based understanding of psychiatric disorders. This will also help in developing new paradigms, similar to those inspired by other neuro-modulatory interventions.[90]

So far, among psychiatric disorders, tVNS has been tried primarily on depression. Although stimulation parameters, site, and duration vary greatly, 2–4 weeks of tVNS may reduce the severity of depression. In epilepsy, about 5–12 months of tVNS have been required to decrease seizure frequency. Furthermore, tVNS has been shown to improve quality of life, mood, sleep, autonomic functioning, systolic blood pressure, headache, and tinnitus.[4] These results are encouraging to further probe tVNS in psychiatric disorders.

tVNS

VNS is of three types: iVNS, percutaneous, and non-invasive/transcutaneous.[4] In iVNS, an electrode, the battery, and the pulse generator are placed inside an implantable device, which is surgically attached to the left VN. The device can be controlled from the outside.[88] In percutaneous VNS, minimally invasive needle electrodes are fixed at areas around the ear that are innervated by the VN. It has been used mainly in pain-related syndromes.[91] The tVNS uses the cutaneous nerves at the cervical region or the ABVN at the ear to be electrically stimulated. For cervical tVNS, the sternocleidomastoid muscle is targeted for the stimuli to reach through the skin, fascia, and muscular structures to the VN. About 80% of the vagal fibres at the cervical region are unmyelinated type C fibres. However, these may not be stimulated during tVNS as painful sensations are not associated during tVNS.[1,14] The control over whether it stimulated the afferent or efferent fibres is thus lost, making

it less precise.[92,93] The stimulation site for ABVN is debated between cymba concha and tragus, with most using the ear lobe for sham stimulation.[4,89,91]

The parameters of stimulation of tVNS are not yet well formulated.[4,89,92] Most tVNS studies use parameters ranging between 1.5 Hz and 30 Hz of frequency (although as high as 120 Hz frequency has also been used), around 0.25–1 microsecond wave width, intensity within 2–6 mA, based on the subject's tolerability, for various lengths of time from 20 min to few hours and alternative on and off time of stimulations. The devices used are mostly handheld for cervical tVNS and attached to the ear for ABVN.[4,5,94-96]

It is important to note that the impact of tVNS should be physiologically informed, for example, cVNS targets efferent fibres, whereas ta-VNS targets afferent fibres exclusively.[4,91] Likewise, stimulating the afferent or efferent fibres in animal models has shown distinguishably differential effects on inflammatory systems, ANS and oxytocin release.[64,65] However, more electrophysiological studies are required to tease out fibre-specific effects of tVNS to fully understand the required stimulation parameters and their utility in clinical psychiatric conditions. The significant advantage of tVNS over iVNS is the safety and tolerability profile.[5] Overall, iVNS implantation is a safe minor surgical procedure and surgery-related risks are seen in about 8% of procedures.[89] Serious complications such as post-operative infection, hematoma and vocal cord palsy are <2%. The left side is generally favoured, as the right side innervates the sinoatrial node and can theoretically cause arrhythmias. However, iVNS also has about 4% of hardware-related problems such as lead fracture, malfunction, or disconnection.[97] Common side effects unrelated to the surgical procedure and hardware are coughs, hoarseness, change in voice, pain, and paraesthesia.[88] Although not shown to be harmful in tVNS, the left VN is still preferred. The most common side effect of tVNS is local skin irritation, headache, and nasopharyngitis. In trials, <3% of the subjects drop out due to complications.[5] Cervical tVNS may lead to temporary painless, mild facial twitching.[91]

FUTURE DIRECTION

The current availability and increasing use of tVNS should be utilised in future studies to test its effects on overall well-being, cognition, inflammatory system, ANS, brain circuits, and psychiatric disorders. It can probably be safely used in investigational and therapeutic studies and may help to determine the causal role of VN in neuropsychiatric disorders. This will enrich our knowledge regarding psychophysiology and will help to bridge the gap between theoretical foundations and the clinical utility of this neuromodulation technique in psychiatry.

CONCLUSION

The VN plays a vital role in neuropsychiatric disorders. Newer tVNS techniques provide opportunities to explore the etiopathological and therapeutic role of the VN in these disorders. Neurophysiologically-oriented research, therefore, can inform clinical decision-making to delineate the potential uses of VNS.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation

The author(s) confirms that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI.

REFERENCES

1. Kenny BJ, Bordoni B. Neuroanatomy, cranial nerve 10 (vagus nerve). In: StatPearls. Treasure Island, FL: StatPearls Publishing. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537171 [Last accessed on 2021 Jun 09].
2. Howland RH. Vagus nerve stimulation. Curr Behav Neurosci Rep 2014;1:64-73.
3. Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex--linking immunity and metabolism. Nat Rev Endocrinol 2012;8:743-54.
4. Farmer AD, Strzelczyk A, Finisguerra A, Gourine AV, Gharabaghi A, Hasan A, *et al.* International consensus based review and recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (Version 2020). Front Hum Neurosci 2021;14:568051.
5. Redgrave J, Day D, Leung H, Laud PJ, Ali A, Lindert R, *et al.* Safety and tolerability of transcutaneous vagus nerve stimulation in humans; a systematic review. Brain Stimul 2018;11:1225-38.
6. Mussa BM, Verberne AJ. The dorsal motor nucleus of the vagus and regulation of pancreatic secretory function. Exp Physiol 2013;98:25-37.
7. Rea P. Vagus nerve. In: Clinical anatomy of the cranial nerves. Ch. 10. San Diego: Academic Press; 2014. p. 105-16.
8. Snell RS. Clinical anatomy by regions. Philadelphia, PA: Lippincott Williams and Wilkins; 2011.

9. Petko B, Tadi P. Neuroanatomy, nucleus ambiguus. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547744 [Last accessed on 2020 Jan 26].
10. Campbell WW. DeJong's the neurologic examination. Philadelphia, PA: Lippincott Williams and Wilkins; 2012.
11. Bonaz B, Sinniger V, Pellissier S. The vagus nerve in the neuro-immune axis: Implications in the pathology of the gastrointestinal tract. Front Immunol 2017;8:1452.
12. McCorry LK. Physiology of the autonomic nervous system. Am J Pharm Educ 2007;71:78.
13. Waxenbaum JA, Reddy V, Varacallo M. Anatomy, autonomic nervous system. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. Available from: http://www.ncbi.nlm.nih.gov/books/NBK539845 [Last accessed on 2020 Jan 26].
14. Qing KY, Wasilczuk KM, Ward MP, Phillips EH, Vlachos PP, Goergen CJ, *et al*. B fibers are the best predictors of cardiac activity during vagus nerve stimulation: Qing, vagal B fiber activation and cardiac effects. Bioelectron Med 2018;4:5.
15. McAllen RM, Shafton AD, Bratton BO, Trevaks D, Furness JB. Calibration of thresholds for functional engagement of vagal A, B and C fiber groups *in vivo*. Bioelectron Med (Lond) 2018;1:21-7.
16. Ludwig RJ, Welch MG. Darwin's other dilemmas and the theoretical roots of emotional connection. Front Psychol 2019;10:683.
17. Porges SW. The polyvagal theory: Neurophysiological foundations of emotions, attachment, communication, and self-regulation (Norton series on interpersonal neurobiology). New York: W. W. Norton and Company; 2011.
18. Colzato LS, Sellaro R, Beste C. Darwin revisited: The vagus nerve is a causal element in controlling recognition of other's emotions. Cortex 2017;92:95-102.
19. Porges SW, Doussard-Roosevelt JA, Maiti AK. Vagal tone and the physiological regulation of emotion. Monogr Soc Res Child Dev 1994;59:167-86.
20. Porges SW. The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. Cleve Clin J Med 2009;76 Suppl 2:S86-90.
21. Wiest G. Neural and mental hierarchies. Front Psychol 2012;3:516.
22. MacLean PD. The triune brain in conflict. Psychother Psychosom 1977;28:207-20.
23. MacLean PD, George MS. The triune brain in evolution: Role in paleocerebral functions. Cogn Behav Neurol 1992;5:68.
24. Valenza G, Sclocco R, Duggento A, Passamonti L, Napadow V, Barbieri R, *et al*. The central autonomic network at rest: Uncovering functional MRI correlates of time-varying autonomic outflow. Neuroimage 2019;197:383-90.
25. Benarroch EE. The central autonomic network: Functional organization, dysfunction, and perspective. Mayo Clin Proc 1993;68:988-1001.
26. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 2007;74:224-42.
27. Thayer JF, Sternberg E. Beyond heart rate variability: Vagal regulation of allostatic systems. Ann N Y Acad Sci 2006;1088:361-72.
28. Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research - recommendations for experiment planning, data analysis, and data reporting. Front Psychol 2017;8:213.
29. Laborde S, Mosley E, Mertgen A. Vagal tank theory: The three Rs of cardiac vagal control functioning - resting, reactivity, and recovery. Front Neurosci 2018;12:458.
30. Grossman P, Taylor EW. Toward understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. Biol Psychol 2007;74:263-85.
31. Shaffer F, Meehan ZM. Practical guide to resonance frequency assessment for heart rate variability biofeedback. Front Neurosci 2020;14:570400.
32. Lehrer PM, Gevirtz R. Heart rate variability biofeedback: How and why does it work? Front Psychol 2014;5:756.
33. McCraty R, Childre D. Coherence: Bridging personal, social, and global health. Altern Ther Health Med 2010;16:10-24.
34. McCraty R, Zayas MA. Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being. Front Psychol 2014;5:1090.
35. McCraty R, Mike A, Tomasino D, Bradley RT. The coherent heart heart-brain interactions, psychophysiological coherence, and the emergence of system-wide Order. Integral Rev 2009;5:10-115.
36. Bradley RT, McCraty R, Atkinson M, Tomasino D, Daugherty A, Arguelles L. Emotion self-regulation, psychophysiological coherence, and test anxiety: Results from an experiment using electrophysiological measures. Appl Psychophysiol Biofeedback 2010;35:261-83.
37. Neuser MP, Teckentrup V, Kühnel A, Hallschmid M, Walter M, Kroemer NB. Vagus nerve stimulation boosts the drive to work for rewards. Nat Commun 2020;11:3555.
38. Perez SM, Carreno FR, Frazer A, Lodge DJ. Vagal nerve stimulation reverses aberrant dopamine system function in the methylazoxymethanol acetate rodent model of schizophrenia. J Neurosci 2014;34:9261-7.
39. Breit S, Kupferberg A, Rogler G, Hasler G. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Front Psychiatry 2018;9:44.
40. Hulsey DR, Shedd CM, Sarker SF, Kilgard MP, Hays SA. Norepinephrine and serotonin are required for vagus nerve stimulation directed cortical plasticity. Exp Neurol 2019;320:112975.
41. Li Y, Zhong W, Wang D, Feng Q, Liu Z, Zhou J, *et al*. Serotonin neurons in the dorsal raphe nucleus encode reward signals. Nat Commun 2016;7:10503.
42. Weber I, Niehaus H, Krause K, Molitor L, Peper M, Schmidt L, *et al*. Trust your gut: Vagal nerve stimulation in humans improves reinforcement learning. Brain Commun 2021;3:fcab039.
43. Berger A, Vespa S, Dricot L, Dumoulin M, Iachim E, Doguet P, *et al*. How is the norepinephrine system involved in the antiepileptic effects of vagus nerve stimulation? Front Neurosci 2021;15:790943.
44. Corsi-Zuelli FM, Brognara F, Quirino GF, Hiroki CH, Fais RS, Del-Ben CM, *et al*. Neuroimmune interactions in schizophrenia: Focus on vagus nerve stimulation and activation of the alpha-7 nicotinic acetylcholine receptor. Front Immunol 2017;8:618.
45. de Jonge WJ, Ulloa L. The alpha7 nicotinic acetylcholine

receptor as a pharmacological target for inflammation. Br J Pharmacol 2007;151:915-29.
46. Partosoedarso ER, Young RL, Blackshaw LA. GABA(B) receptors on vagal afferent pathways: Peripheral and central inhibition. Am J Physiol Gastrointest Liver Physiol 2001;280:G658-68.
47. Hou X, Rong C, Wang F, Liu X, Sun Y, Zhang HT. GABAergic system in stress: Implications of GABAergic neuron subpopulations and the gut-vagus-brain pathway. Neural Plast 2020;2020:8858415.
48. Talman WT, Granata AR, Reis DJ. Glutamatergic mechanisms in the nucleus tractus solitarius in blood pressure control. Fed Proc 1984;43:39-44.
49. Perrone MH. Biochemical evidence that L-glutamate is a neurotransmitter of primary vagal afferent nerve fibers. Brain Res 1981;230:283-93.
50. Dreifuss JJ, Raggenbass M, Charpak S, Dubois-Dauphin M, Tribollet E. A role of central oxytocin in autonomic functions: Its action in the motor nucleus of the vagus nerve. Brain Res Bull 1988;20:765-70.
51. Everett NA, Turner AJ, Costa PA, Baracz SJ, Cornish JL. The vagus nerve mediates the suppressing effects of peripherally administered oxytocin on methamphetamine self-administration and seeking in rats. Neuropsychopharmacology 2021;46:297-304.
52. Musha T, Satoh E, Koyanagawa H, Kimura T, Satoh S. Effects of opioid agonists on sympathetic and parasympathetic transmission to the dog heart. J Pharmacol Exp Ther 1989;250:1087-91.
53. Qureshi IS, Datta-Chaudhuri T, Tracey KJ, Pavlov VA, Chen AC. Auricular neural stimulation as a new non-invasive treatment for opioid detoxification. Bioelectron Med 2020;6:7.
54. Randich A, Gebhart GF. Vagal afferent modulation of nociception. Brain Res Brain Res Rev 1992;17:77-99.
55. Ziomber A, Thor P, Krygowska-Wajs A, Załęcki T, Moskała M, Romańska I, *et al.* Chronic impairment of the vagus nerve function leads to inhibition of dopamine but not serotonin neurons in rat brain structures. Pharmacol Rep 2012;64:1359-67.
56. Manta S, El Mansari M, Debonnel G, Blier P. Electrophysiological and neurochemical effects of long-term vagus nerve stimulation on the rat monoaminergic systems. Int J Neuropsychopharmacol 2013;16:459-70.
57. Surowka AD, Krygowska-Wajs A, Ziomber A, Thor P, Chrobak AA, Szczerbowska-Boruchowska M. Peripheral vagus nerve stimulation significantly affects lipid composition and protein secondary structure within dopamine-related brain regions in rats. Neuromolecular Med 2015;17:178-91.
58. Malbert CH, Genissel M, Divoux JL, Henry C. Chronic abdominal vagus stimulation increased brain metabolic connectivity, reduced striatal dopamine transporter and increased mid-brain serotonin transporter in obese miniature pigs. J Transl Med 2019;17:78.
59. McVey Neufeld KA, Bienenstock J, Bharwani A, Champagne-Jorgensen K, Mao Y, West C, *et al.* Oral selective serotonin reuptake inhibitors activate vagus nerve dependent gut-brain signalling. Sci Rep 2019;9:14290.
60. Zinner MJ, Jaffe BM, DeMagistris L, Dahlstrom A, Ahlman H. Effect of cervical and thoracic vagal stimulation on luminal serotonin release and regional blood flow in cats. Gastroenterology 1982;82:1403-8.
61. Roosevelt RW, Smith DC, Clough RW, Jensen RA, Browning RA. Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. Brain Res 2006;1119:124-32.
62. Follesa P, Biggio F, Gorini G, Caria S, Talani G, Dazzi L, *et al.* Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. Brain Res 2007;1179:28-34.
63. Raedt R, Clinckers R, Mollet L, Vonck K, El Tahry R, Wyckhuys T, *et al.* Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. J Neurochem 2011;117:461-9.
64. Farrand AQ, Verner RS, McGuire RM, Helke KL, Hinson VK, Boger HA. Differential effects of vagus nerve stimulation paradigms guide clinical development for Parkinson's disease. Brain Stimul 2020;13:1323-32.
65. Stock S, Uvnäs-Moberg K. Increased plasma levels of oxytocin in response to afferent electrical stimulation of the sciatic and vagal nerves and in response to touch and pinch in anaesthetized rats. Acta Physiol Scand 1988;132:29-34.
66. Iwasaki Y, Maejima Y, Suyama S, Yoshida M, Arai T, Katsurada K, *et al.* Peripheral oxytocin activates vagal afferent neurons to suppress feeding in normal and leptin-resistant mice: A route for ameliorating hyperphagia and obesity. Am J Physiol Regul Integr Comp Physiol 2015;308:R360-9.
67. O'Leary OF, Ogbonnaya ES, Felice D, Levone BR, Conroy LC, Fitzgerald P, *et al.* The vagus nerve modulates BDNF expression and neurogenesis in the hippocampus. Eur Neuropsychopharmacol 2018;28:307-16.
68. Jin Y, Sun LH, Yang W, Cui RJ, Xu SB. The role of BDNF in the neuroimmune axis regulation of mood disorders. Front Neurol 2019;10:515.
69. Rosso P, Iannitelli A, Pacitti F, Quartini A, Fico E, Fiore M, *et al.* Vagus nerve stimulation and neurotrophins: A biological psychiatric perspective. Neurosci Biobehav Rev 2020;113:338-53.
70. Staats P, Giannakopoulos G, Blake J, Liebler E, Levy RM. The use of non-invasive vagus nerve stimulation to treat respiratory symptoms associated with COVID-19: A theoretical hypothesis and early clinical experience. Neuromodulation 2020;23:784-8.
71. Tsaava T, Datta-Chaudhuri T, Addorisio ME, Masi EB, Silverman HA, Newman NE, *et al.* Specific vagus nerve stimulation parameters alter serum cytokine levels in the absence of inflammation. Bioelectron Med 2020;6:8.
72. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: A meta-analysis of efficacy and predictors of response. J Neurosurg 2011;115:1248-55.
73. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res 2018;11:203-13.
74. Busch V, Zeman F, Heckel A, Menne F, Ellrich J, Eichhammer P. The effect of transcutaneous vagus nerve stimulation on pain perception--an experimental study. Brain Stimul 2013;6:202-9.
75. Ruffle JK, Coen SJ, Giampietro V, Williams SC, Aziz Q, Farmer AD. Preliminary report: Parasympathetic tone links to functional brain networks during the anticipation and experience of visceral pain. Sci Rep 2018;8:13410.

76. Tu Y, Fang J, Cao J, Wang Z, Park J, Jorgenson K, *et al.* A distinct biomarker of continuous transcutaneous vagus nerve stimulation treatment in major depressive disorder. Brain Stimul 2018;11:501-8.
77. Wang Z, Fang J, Liu J, Rong P, Jorgenson K, Park J, *et al.* Frequency-dependent functional connectivity of the nucleus accumbens during continuous transcutaneous vagus nerve stimulation in major depressive disorder. J Psychiatr Res 2018;102:123-31.
78. Zobel A, Joe A, Freymann N, Clusmann H, Schramm J, Reinhardt M, *et al.* Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: An exploratory approach. Psychiatry Res 2005;139:165-79.
79. Ashare RL, Sinha R, Lampert R, Weinberger AH, Anderson GM, Lavery ME, *et al.* Blunted vagal reactivity predicts stress-precipitated tobacco smoking. Psychopharmacology (Berl) 2012;220:259-68.
80. Bremner JD, Wittbrodt MT, Gurel NZ, Shandhi MH, Gazi AH, Jiao Y, *et al.* Transcutaneous cervical vagal nerve stimulation in patients with posttraumatic stress disorder (PTSD): A pilot study of effects on PTSD symptoms and interleukin-6 response to stress. J Affect Disord Rep 2021;6:100190.
81. Kar SK, Sarkar S. Neuro-stimulation techniques for the management of anxiety disorders: An update. Clin Psychopharmacol Neurosci 2016;14:330-7.
82. Büttiker P, Weissenberger S, Ptacek R, Stefano GB. Interoception, trait anxiety, and the gut microbiome: A cognitive and physiological model. Med Sci Monit 2021;27:e931962.
83. Weng HY, Feldman JL, Leggio L, Napadow V, Park J, Price CJ. Interventions and manipulations of interoception. Trends Neurosci 2021;44:52-62.
84. Finisguerra A, Crescentini C, Urgesi C. Transcutaneous vagus nerve stimulation affects implicit spiritual self-representations. Neuroscience 2019;412:144-59.
85. Manning KE, Beresford-Webb JA, Aman LC, Ring HA, Watson PC, Porges SW, *et al.* Transcutaneous vagus nerve stimulation (t-VNS): A novel effective treatment for temper outbursts in adults with Prader-Willi Syndrome indicated by results from a non-blind study. PLoS One 2019;14:e0223750.
86. Briand MM, Gosseries O, Staumont B, Laureys S, Thibaut A. Transcutaneous auricular vagal nerve stimulation and disorders of consciousness: A hypothesis for mechanisms of action. Front Neurol 2020;11:933.
87. Corazzol M, Lio G, Lefevre A, Deiana G, Tell L, André-Obadia N, *et al.* Restoring consciousness with vagus nerve stimulation. Curr Biol 2017;27:R994-6.
88. Ben-Menachem E, Revesz D, Simon BJ, Silberstein S. Surgically implanted and non-invasive vagus nerve stimulation: A review of efficacy, safety and tolerability. Eur J Neurol 2015;22:1260-8.
89. Thompson SL, O'Leary GH, Austelle CW, Gruber E, Kahn AT, Manett AJ, *et al.* Review of parameter settings for invasive and non-invasive vagus nerve stimulation (VNS) applied in neurological and psychiatric disorders. Front Neurosci 2021;15:7098436.
90. Bergmann TO, Hartwigsen G. Inferring causality from noninvasive brain stimulation in cognitive neuroscience. J Cogn Neurosci 2021;33:195-225.
91. Yap JY, Keatch C, Lambert E, Woods W, Stoddart PR, Kameneva T. Critical review of transcutaneous vagus nerve stimulation: Challenges for translation to clinical practice. Front Neurosci 2020;14:284.
92. Badran BW, Brown JC, Dowdle LT, Mithoefer OJ, LaBate NT, Coatsworth J, *et al.* Tragus or cymba conchae? Investigating the anatomical foundation of transcutaneous auricular vagus nerve stimulation (taVNS). Brain Stimul 2018;11:947-8.
93. McIntire LK, McKinley RA, Goodyear C, McIntire JP, Brown RD. Cervical transcutaneous vagal nerve stimulation (ctVNS) improves human cognitive performance under sleep deprivation stress. Commun Biol 2021;4:634.
94. Kaniusas E, Kampusch S, Tittgemeyer M, Panetsos F, Gines RF, Papa M, *et al.* Current directions in the auricular vagus nerve stimulation II - an engineering perspective. Front Neurosci 2019;13:772.
95. Redgrave JN, Moore L, Oyekunle T, Ebrahim M, Falidas K, Snowdon N, *et al.* Transcutaneous auricular vagus nerve stimulation with concurrent upper limb repetitive task practice for poststroke motor recovery: A pilot study. J Stroke Cerebrovasc Dis 2018;27:1998-2005.
96. Sclocco R, Garcia RG, Kettner NW, Fisher HP, Isenburg K, Makarovsky M, *et al.* Stimulus frequency modulates brainstem response to respiratory-gated transcutaneous auricular vagus nerve stimulation. Brain Stimul 2020;13:970-8.
97. Révész D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. J Neurosurg Pediatr 2016;18:97-104.

How to cite this article: Nayok SB, Sreeraj VS, Shivakumar V, Venkatasubramanian G. The vagus nerve in psychiatry: From theories to therapeutic neurostimulation in neuropsychiatric disorders. Indian J Physiol Pharmacol 2023;67:151-62.