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REVIEW

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Noninvasive vagus nerve stimulation in Parkinson's disease: current status and future prospects

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ABSTRACT

Introduction: Parkinson's disease (PD) is a common progressive neurodegenerative disorder with multifactorial etiology. While dopaminergic medication is the standard therapy in PD, it provides limited symptomatic treatment and non-pharmacological interventions are currently being trialed.

Areas covered: Recent pathophysiological theories of Parkinson's suggest that aggregated α-synuclein form in the gut and spread to nuclei in the brainstem via autonomic connections. In this paper, we review the novel hypothesis that noninvasive vagus nerve stimulation (nVNS), targeting efferent and afferent vagal projections, is a promising therapeutic tool to improve gait and cognitive control and ameliorate non-motor symptoms in people with Parkinson's. We conducted an unstructured search of the literature for any studies employing nVNS in PD as well as for studies examining the efficacy of nVNS on improving cognitive function and where nVNS has been applied to co-occurring conditions in PD.

Expert opinion: Evidence of nVNS as a novel therapeutic to improve gait in PD is preliminary, but early signs indicate the possibility that nVNS may be useful to target dopa-resistant gait characteristics in early PD. The evidence for nVNS as a therapeutic tool is, however, limited and further studies are needed in both brain health and disease.

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Cognition; gait; neuroinflammation; Parkinson's disease; vagus nerve stimulation

1. Introduction

Pharmacological intervention forms the mainstay treatment for many neurodegenerative and neuropsychiatric disorders, but this approach carries unwanted side effects. Non-pharmacological alternatives such as electrical stimulation used mostly as an adjunct therapy, has gained considerable interest. Vagus nerve stimulation (VNS) is a neuromodulation technique involving invasive surgical implantation of a generator subcutaneously, providing direct electrical stimulation of the left cervical vagus nerve [1–3]. Implantable VNS (iVNS) sends intermittent electrical currents through a wire wrapped around the vagus nerve. It is more common that the left vagus nerve is stimulated due to the right vagus nerve having greater connections to the heart [1]. The VNS device conveys signals through neural impulses to the central nervous system (CNS) [1]. iVNS is approved by the U.S. Food and Drug Administration (FDA) as an adjunct treatment for drug-resistant epilepsy [4] and in patients with treatment-resistant depression [5]; iVNS is also approved by the European Medicines Agency (EMA) for the latter. Recent randomized controlled trials have additionally shown the potential benefits of iVNS in upper limb motor recovery after stroke when stimulation is paired with rehabilitation therapy [6].

The efficacy of iVNS in preventing and ameliorating symptoms of neurodegenerative and neuropsychiatric disorders has captured interest across several clinical fields, with the number of publications utilizing VNS steadily rising. Due to the potential complications and reported adverse events [7,8], noninvasive VNS (nVNS) devices have also been developed with the aim of stimulating the vagus nerve transcutaneously. With the advent of the noninvasive devices, risk and adverse events associated with the implantable devices such as the cost of medical care accompanying an invasive surgery and intraoperative complications that can include infections, vagus nerve trauma, peritracheal hematoma, damage to the vocal cords and shortness of breath (dyspnea) due to vagus nerve injury [7–9] are minimized or altogether eliminated. Additionally, lead fractures can occur requiring electrode changes [8]. A further advantage of the nVNS devices is that they promote further research in cognitive and clinical neuroscience to objectively identify the technique's mechanisms of action specifically in healthy populations without requiring invasive surgery [10]. To that end, in the translational setting nVNS is becoming an increasingly prevalent tool to assess the effects of this type of neuromodulation on various psychological and physiological processes [10].

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Article highlights

- The known mechanisms of action of nVNS suggest it may impact brain regions and neurotransmitter systems affected by neurodegeneration in PD.
- Recent pathophysiological theories of PD suggest that neurons with Lewy Body pathology may originate in the gut and spread via the vagus nerve to the midbrain with both motor and non-motor symptoms being associated with this occurrence.
- Preliminary evidence highlights proof of concept for a single dose of nVNS to improve dopa-resistant gait characteristics in PD. Evidence for improved cognition and cognitive function in PD is lacking.
- Early results in other disease areas support nVNS as a promising therapeutic tool to improve other non-motor symptoms in PD, such as neuroinflammation, autonomic function, reduced gastroparesis, and fatigue.
- The translational effects of nVNS is an emerging field of study. Considerable work is needed to accurately determine the stimulation type (trans-auricular or trans-cervical) side (left or right), frequency of the stimulation, stimulation intensity, pulse width, cycle duration and waveform shape. Information on dosages is also needed, and future studies should assess the optimal number of treatments, number of doses per day and treatment tolerance. Finally, studies are needed to disentangle whether and how nVNS treatment interacts with pharmacological therapies such as acetylcholinesterase inhibitors.

In principle, two types of nVNS devices are commercially available. Transcutaneous auricular VNS (taVNS) is used to stimulate structures of the outer ear such as the tragus and cymba conchae, which are innervated by the auricular branch of the vagus nerve (ABVN) [11]. By contrast, transcutaneous cervical VNS (tcVNS) is delivered via a hand-held device while indirectly stimulating the (left) cervical branch of the vagus nerve within the carotid sheath [12]. A pressing issue is to identify the most optimal stimulation parameters such as the current intensity (milliamps [mA]), frequency (Hertz [Hz]), pulse width (microseconds [μs]), waveform shape (sine, rectangular), cycle duration (on/off periods) and optimal dosage. Stimulation parameters used in studies employing the taVNS device vary widely (readers are referred to as an excellent and comprehensive review by Farmer and colleagues [10]). The majority of studies utilize monophasic or biphasic rectangular pulses, with a pulse width between 200 and 300 μs, current intensity at 0.5 mA, and a frequency of 25 Hz [10].

The tcVNS device emits a low-voltage 5 kHz sine wave electrical signal bursts lasting 1 ms via two flat stimulation contact surfaces, which permeates the skin and subcutaneous structures [12]. These bursts repeat once every 40 ms (25 Hz frequency) for 120 seconds. Stimulation intensity can be adjusted by the patient, and stimulation can be repeated up to 12 times per day. According to the manufacturer (ElectroCore, Basking Ridge, NJ, USA) their gammaCore® device uses sine waves since these produce less unpleasant skin sensations and are thus better tolerated compared to square waves. tcVNS is currently licensed for the treatment of primary headache, epilepsy, depression, and anxiety.

The most common adverse events related to the use of the noninvasive devices include headaches, nasopharyngitis, dizziness, oropharyngeal, and neck pain, skin irritation [13,14]. The attrition rate due to adverse events is approximately 2.6% in studies employing nVNS [14].

Parkinson's disease (PD) is a neurodegenerative disorder that affects the central, peripheral, and enteric nervous systems and is characterized by both motor and non-motor symptoms of which gait and cognitive impairment are common manifestations [15,16]. Gait and cognition are interrelated both in the general population and in PD [15,16]. Gait problems are observed in all gait domains according to a validated gait model in PD [17,18], while cognitive dysfunction is noted in several cognitive domains including visuospatial, attention, and memory [19]. Deficits in both gait and cognition are consistently associated with falls, reductions in health-related quality of life, healthcare costs, and increased caregiver burden [20,21]. Although dopaminergic (DA) medication is the current gold standard treatment for PD, compelling evidence has shown that patients respond selectively to DA treatment, and both gait and cognitive function continue to progressively decline with time [17,22,23], thus suggesting an alternative pathological basis.

Novel non-pharmacological interventions mitigating both PD-associated gait and cognitive impairments are urgently needed. Due to its clinical properties and widespread effects on Central and Autonomic Nervous Systems (CNS/ANS), VNS may be a suitable therapy in PD as highlighted below in the main body of our manuscript. The effects of nVNS on gait problems in human participants with PD has been demonstrated in three recent publications [24–26]. Furthermore, some recent studies have investigated the clinical efficacy of VNS for reducing symptoms that often occur in PD, including fatigue [27] and gastrointestinal symptoms [28,29], neuropsychiatric disorders [30,31], dementia [32,33] and essential tremor [34] providing further theoretical support. Therefore, the aim of this review was to summarize the current literature on nVNS in PD and provide narrative accounts of its therapeutic potential with an emphasis on its efficacy in improving gait and cognitive control, and the mechanisms of action that may mediate these improvements in this disorder.

2. The vagus nerve: mechanisms of action and importance in Parkinson's disease

The vagus nerve is the tenth cranial nerve and is composed of 20% motor efferent and 80% sensory afferent fibers [35]. It is located on both the right and left side of the body and acts as a bidirectional channel between the CNS and ANS relaying sensory and motor information between systems [35]. The descending fibers of the vagus nerve traverse and innervate directly or indirectly major internal organs including the heart, spleen, and the gastrointestinal tract, regulating cardiovascular function, inflammatory response, and gastric emptying efferent effects, respectively [36–38]. The vagus nerve is therefore essential in the maintenance of parasympathetic system function and homeostasis.

The motor symptoms of PD emerge due to dysfunction of afferent projection terminals within the striatum and a progressive loss of nigral DA neurons associated with intracellular Lewy bodies (LBs) containing aggregated α-synuclein [39]. Interest in the vagus nerve in PD is relatively longstanding, with Braak and colleagues [40,41] postulating that α-synuclein pathology may spread via the vagus nerve from

the GI tract to the midbrain. However, the transfer of LB pathology may not be random but may spread from the medulla oblongata in the brainstem and olfactory nuclei in the caudo-rostral direction to further susceptible structures within the brainstem, limbic system, and finally neocortical regions [41]. This was supported by recent work in a mouse model of PD, where pathogenic α-synuclein injected into an area of the gut richly innervated by the vagus nerve, was found to spread to the dorsal motor nucleus of the vagus (DMNV), locus coeruleus (LC), amygdala, substantia nigra (SN) and, subsequently, the cortex over time [42]. This was associated with degeneration of DA neurons, as well as motor and non-motor symptoms. Truncal vagotomy precluded the symptoms, neurodegeneration and α-synuclein pathology within the brain. However, one recent postmortem study did not demonstrate a difference between intestinal α-synuclein in PD patients and control participants [43], which may challenge this rationale. Potential explanations for the discrepancy between the studies include sampling from different areas of the GI tract, diverse peripheral neuroanatomy in the different populations, and different immunohistochemical staining techniques.

A further contentious issue is where Lewy pathology begins within the brain. This was the subject of a recent multimodal imaging study with the authors proposing 'brain-first versus body-first' PD subtypes [44]. Based on the model proposed by Horsager and colleagues, the trajectory of LB pathology described above is considered as the 'body-first' subtype. By contrast, the reverse trajectory characterizes the 'brain-first' subtype where aggregated α-synuclein may arise in the olfactory tubercle within the brain and descend into the peripheral ANS via structures of the brainstem including the LC [44]. Both subtypes seem to demonstrate alterations in structures and functions subserved by the vagus nerve. There is some evidence that the structural integrity of the vagus nerve, measured using high-resolution ultrasound, may be altered in PD. Some studies have found that both left and right vagus nerves are significantly smaller in patients relative to age-matched controls [45–47], while others have shown a comparable size of the vagus nerve between patients and controls [48–51].

Further alterations associated with cardinal symptoms of PD including gait problems and cognitive dysfunction arise due to alterations in cholinergic neurotransmission in the cholinergic basal forebrain, particularly in the nucleus basalis of Meynert (nbM) and the pedunculopontine nucleus (PPN) in the brainstem [52–54], and serotonergic neurons in the raphe nuclei [55], decreased neurotropic factor signaling in the SN and basal ganglia [56] and possibly due to an abnormal inflammatory response in the brain [57]. This suggests that PD is underpinned by multi-system pathology subserved by several neurotransmitter systems in addition to age-related neurodegeneration that may be related to the function of the vagus nerve.

2.1. Imaging and VNS in humans

The neural correlates of VNS remain enigmatic, and imaging studies have produced somewhat inconsistent results. The low temporal and spatial resolutions of the imaging modalities used, varying stimulation parameters, limited sample sizes, and the clinical populations assessed are all potentially confounding factors. In healthy volunteers undergoing nVNS, the aim is to measure changes in the blood oxygenation level dependent (BOLD) response in vagal afferent pathway target regions. To date, at least eight studies using whole-brain exploratory analysis have been reported [58–65]. Using taVNS, some [59–62] but not others [58,63] showed increased BOLD response in the nucleus tractus solitarius (NTS) and LC. Conversely, Kraus and colleagues [59] reported decreased BOLD response in both regions during taVNS. Across these studies, increased activity (during taVNS relative to rest or sham stimulation) has been found in regions encompassing salience (insula, anterior cingulate), basal ganglia (caudate nucleus, putamen), thalamic, and cerebellar brain networks. By contrast, deactivation was observed in the limbic system and temporal lobe when sham stimulation has been compared to active stimulation. It is noteworthy that the exact neural connections of the ABVN are not known. The tragus is innervated, for example, only by the great auricular nerve and the auriculotemporal nerve, not the vagus nerve [66].

To our knowledge, only one study has investigated the dynamic, online changes in brain function during tcVNS. Frangos and Komisaruk [65] placed two electrodes over the *right* cervical vagus nerve in 13 healthy participants undergoing fMRI imaging. In comparison to pre-nVNS rest and reference stimulation (placed on the *right* sternocleidomastoid muscle), 2 min of continuous tcVNS elicited increased BOLD response in several regions of the forebrain that contain cholinergic neurons or receive dense cholinergic projections from the nbM including bilateral dorsolateral prefrontal cortex (DLPFC), caudate nucleus, and thalamus, left (contralateral) visceral area of the postcentral gyrus, and cerebellum (see Figure 1). During an analysis focused on the lower brainstem, greater BOLD response was noted in the ipsilateral nucleus of solitary tract (NTS, ipsilateral to the stimulation), bilateral parabrachial complex (PB), as well as in SN and ventral tegmental area (VTA) during stimulation relative to control. This study additionally showed that activity in the SN (the source of the nigrostriatal pathway transmitting DA from SN to caudate and putamen; an area severely affected in PD) and VTA (from which DA is transmitted to ventral striatum [mesolimbic pathway] and to PFC [mesocortical pathway]; an area less affected in PD) outlasted the period of tcVNS stimulation. As such, tcVNS may be better suited for targeting key regions of neurodegeneration in PD that underpin gait and cognitive impairments. Further studies are, however, warranted.

2.2. VNS and norepinephrine

Alterations in the complex interplay between DA, norepinephrine (NE), and serotonergic systems, in addition to cholinergic neurotransmission, have been attributed to both motor and non-motor functions in PD [40,67,68]. This is supported by *post mortem* studies that have revealed profound cell loss and LBs in the LC [69,70] leading to the theory that neurodegeneration of LC in addition to the raphe nuclei – containing serotonergic neurons – may precede that of DA-SN neurons in some cases [40].

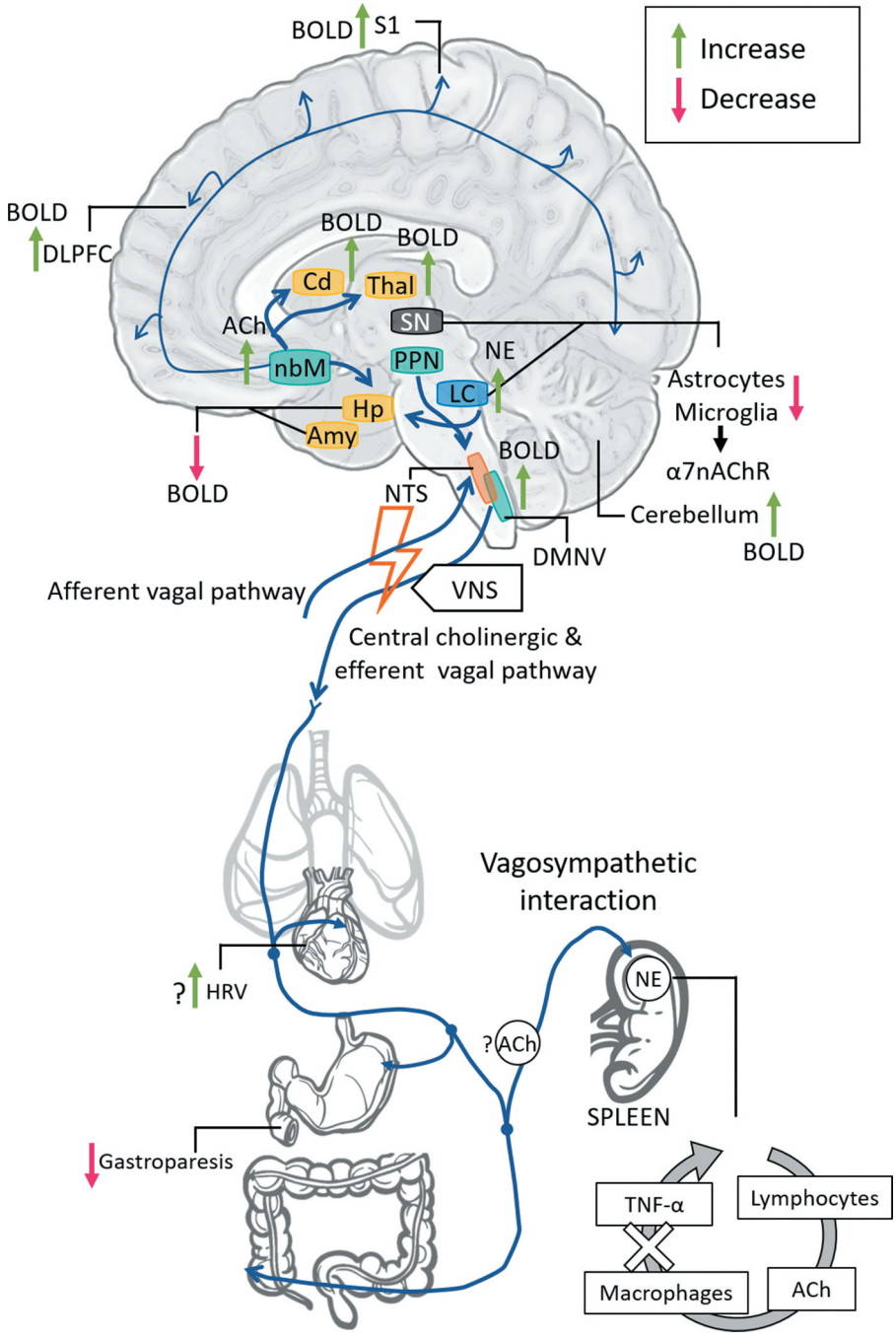

Figure 1. **VNS mechanisms of action and physiological effects**. Abbr. ACh, acetylcholine; Amy, amygdala; BOLD, blood oxygenation level dependant; Cd, caudate; DMNV, dorsal motor nucleus of the vagus; DLFPC, dorsolateral prefrontal cortex; Hp, hippocampus; HRV, heart-rate variability; LC, locus coeruleus; nbM, nucleus basalis of Meynert; NE, norepinephrine; NTS, nucleus tractus solitarius; PPN, pedunculopontine nucleus; S1, primary somatosensory cortex; Thal, thalamus; TNF- α, tumor necrosis factor-α; VNS, vagus nerve stimulation; Note, the figure is partly adapted from [36] and [92]. Icons used in the figure are provided gratis by https://www.freepik.com.

VNS may modulate LC-NE neurons via afferent projections to the NTS [71], a sensory nucleus located in the brainstem medulla [1]. According to George [1], the NTS relays afferent sensory information to cortical and subcortical brain structures using an autonomic feedback loop, via direct projections to nuclei in the medulla and through arising pathways via the LC and PB that terminate in the forebrain [1]. The LC is the main site for synthesis of NE in the brain with a neuroprotective role [72,73]. Transient, intensity-dependent increase in brain NE is observed following iVNS [74,75].

The LC projects to all levels of the forebrain, including limbic structures (thalamus, amygdala, hippocampus) [76]. These regions play a central role in higher cognitive and affective processes [76]. Visceral information from the vagus nerve is furthermore relayed to the hypothalamus, insular cortex, and the anterior cingulate cortex [1]. The LC additionally has reciprocal connections with the PFC and is therefore believed to play a putative role in PFC cognitive functions such as working memory [77]. VNS has been shown to induce mood and emotion enhancing effects potentially due to LC's extensive connections with limbic

structures, particularly the amygdala, in addition to the amygdala's main output pathway, the bed nucleus of stria terminalis [76]. LC-NE projections also reach the cholinergic nbM in the basal forebrain [78] which may cause the upregulation of ACh via stimulation of excitatory α1- and β1-adrenoceptors [79].

2.3. VNS cholinergic activity and inflammation

There is some evidence from animal models implicating acetylcholine (ACh) as a mechanism of action in VNS [80,81]. Attenuation of VNS following the application of the muscarinic agonist scopolamine in a rat model [80] and after lesioning the nucleus basalis of Meynert (nbM) [82] corroborates this.

ACh is a neurotransmitter and a neuromodulator that is pivotal for various cognitive, sensory, and motor functions [83,84], and is thought to mitigate the production of pro-inflammatory cytokines [85]. ACh acts through two receptors in the CNS, ionotropic nicotinic receptors (nAChRs) and metabotropic muscarinic receptors (mAChRs) [84].

Increased density of astrocytes and active microglia have been observed in PD, which supports the theory that PD may be a disorder of neuroinflammation [57,86]. When neuroinflammation begins in PD relative to neurodegeneration is unsubstantiated [57], but neurodegeneration is exacerbated under persistent neuroinflammation [57,87]. Vagal efferents originate in the DMNV, which lies in the medulla, adjacent to the NTS and receives the majority of processed NTS sensory signals [88]. The primary neurotransmitter of DMNV neurons is ACh, and DMNV neurons together with ACh play a key role in inhibiting neuroinflammation via the cholinergic anti-inflammatory pathway [36–38,89]. It is therefore not surprising that the vagus nerve is sensitive to pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6 and IL-18 and tumor necrosis factor-α (TNF-α) but not IL-10 [85] and that VNS has anti-inflammatory effects possibly by upregulating cholinergic neurotransmission, inhibiting the production of both IL and TNF-α [38,85]. It has also been theorized that this process occurs in the spleen via the vagus nerve using ACh (through α7nAChR subtype) and a vagosympathetic interaction [36,90,91] – see Figure 1. Another example of the anti-inflammatory effects of VNS occurs in the GI tract [36,92]. These effects are also mediated via the α7nAChR subtype [85,93]. However, the exact mechanisms underpinning the interaction between the vagus nerve, spleen, and GI tract is debated [36] and the evidence in PD is limited [37]. We refer the reader to Bonaz and colleagues [36] and Pavlov and Tracey [92] for an excellent discussion on this topic.

In PD, DMNV neurons are highly susceptible to neurodegeneration, and contain phosphorylated α-synuclein [40] leading to neuroinflammatory processes [94]. Farrand and colleagues [95–97] showed that VNS reduced the number of astrocytes and microglia, as well as reverting microglia back to their inactive state in a rat model of PD. Furthermore, the authors showed that VNS reduced aggregated α-synuclein in the SN. These effects are most strongly induced during high-frequency microburst VNS and restores neurodegenerative and anti-inflammatory effects to levels comparable to unlesioned control animals [96]. The evidence on how these effects are exerted is limited but increased brain-derived neurotrophic factor (BDNF) and an activation of central α7nAChRs has been suggested [93,95]. Jiang and colleagues [98] furthermore showed that taVNS in PD model rats reduced levels of TNF-α and IL-1β (pro-inflammatory) cytokines and increased levels of α7nAChRs. In humans, one study demonstrated that following tcVNS for 26-days, patients with Sjögren's syndrome demonstrated significant reduction of cytokines in blood including TNF-α and IL-1β [27]. Findings from a recent study suggests that repeated tcVNS stimulation over a 30-day period reduces TNF-α and increases the concentration of BDNF in blood serum in human PD participants [26].

The evidence presented above lends credence to the proposal that VNS may boost the cholinergic system and modulate neuroinflammation in PD.

3. VNS may mitigate gait problems in PD

Gait impairments in PD appear early in the course of the disease, progressively worsen with disease severity, and respond only selectively to treatment [17,99]. They have significant consequences, as discrete gait characteristics predict future falls even in those who are falls naïve [100]. Progression of discrete gait impairments (such as step time variability and step length variability) are evident in early disease despite optimal dopaminergic treatment [23]. This reflects the contemporary view of PD as a complex multisystem disorder in which core impairments are underpinned by deficits in multiple neurotransmitter systems, as well as age-related neurodegeneration.

Cognitive impairment contributes to early gait deficits [101], and conversely, gait impairments predict cognitive decline in early PD [102]. Both cognitive deficit and gait impairment in PD may be in part underpinned by systematic alterations in cholinergic neurotransmission [53,103–106] in addition to neurodegeneration of the nigrostriatal DA pathway [103]. The cholinergic nbM and PPN in addition to intrinsic cholinergic neurons in the hippocampus, striatum, cortex, the medial habenula, and cerebellum constitute the principal sources of cholinergic projections in the brain [107–109]. Loss of cholinergic neurons in both the nbM and PPN in PD is extensive [110,111]. Improvements in gait and postural control in PD are observed following deep-brain stimulation (DBS) of the nbM and PPN [112,113] Furthermore, acetylcholinesterase inhibitors (AChEI), aimed at boosting the output of cholinergic neurons within the nbM, are under investigation in the management of gait impairments in PD [114].

3.1. VNS and locomotion in animals

At least five studies have assessed the effects of VNS on gait in animal models of PD. These have shown that chronic iVNS [95–97,115] or taVNS [98] improves locomotion or locomotor asymmetry relative to animals receiving no VNS (indexed by the cylinder test assessing forelimb akinesia and increased total distance traveled [95–97,115], increased latency to time to fall using the rotarod task, and time to traverse on the

beam-walking test [98]). In these studies, the improvement in locomotion coincided with a reduction in markers of neuroinflammation, increased density of Tyrosine Hydroxylase (TH)-positive cells – an enzyme which aids in the conversion of L-tyrosine to L-DOPA – in both SN and LC [95–98,115] in addition to reduced α-synuclein in SN [95–98]. In relation to this, VNS was also used in conjunction with forearm training in non-parkinsonian rats [82]. This study showed that VNS paired with training led to increased cortical motor maps relative to untrained animals – an indicator of neuroplasticity. By contrast, in animals with selective lesions of cholinergic nbM neurons, VNS paired with forearm training did not lead to increased cortical representation of the forelimb area indicating that cholinergic pathways are critical for this reorganization to occur [82]. One caveat of this study, however, was that motor performance in both groups (lesioned and non-lesioned nbM) was similar, suggesting that forelimb cortical representation cannot solely explain functional activity.

Farrand and colleagues assessed three stimulation frequencies and cycle durations in PD animal models [96] (see Table 1 for further details). The three stimulation parameters included low-frequency VNS, high-frequency VNS, and microburst biomimetic VNS. All groups received identical current intensity of 0.75 mA. In short, all groups (relative to the sham group receiving no stimulation) showed improvements in all assessments, but a trend for the microburst biomimetic VNS to have the greatest effects [96].

In a recent study by another group, Kin and colleagues [115] used variable stimulation intensity but identical pulse frequency, pulse width, and cycle duration (see Table 1) with stimulation administered for 14 days. Results indicated that VNS had the greatest effect in animals who received moderate intensity stimulation (0.25 and 0.5 mA) since these animals showed less forelimb akinesia relative to animals receiving low or high-intensity stimulation. In this study [115], stimulation of the VN was initiated immediately following lesioning (using 6-OHDA, a neurotoxin affecting DA and NE neurons in the brain). In contrast, Farrand and colleagues used a double lesion approach and mimicked the PD pathology trajectory first by causing LC-NE depletion (DSP-6, another neurotoxin) followed by SN-DA lesioning (6-OHDA) 7 days later. VNS therapy then began 11 days following the SN-DA lesioning [95–97].

3.2. Preliminary evidence for VNS effect on locomotion in PD

Pilot studies in human subjects with PD have explored the use of acute and chronic tcVNS on gait improvement. In one study, 19 participants with mild-to-moderate PD, with and without freezing of gait (FOG) were assessed using an instrumented walkway technology pre- and post-stimulation applied twice to the *left* side of the neck. Step length, count, velocity, and stride velocity variability were all found to be improved in participants, while in patients with FOG the number of steps taken to turn was significantly reduced [25]. In a recent randomized sham-controlled study, Morris and colleagues [24] studied 30 participants with PD. Participants received either a single dose of active or sham tcVNS to the *left* side of the neck in addition to their usual treatment. Gait was measured both pre- and post-stimulation. Both step time and step length variability decreased in participants in the active group relative to

Table 1. Stimulation location, parameters and duration for all studies assessing the efficacy of VNS in people with Parkinson's and Parkinson's model rats.

Author (year)	Stimulation location	Stimulation parameters	Stimulation duration	Additional information.
Morris, et al. [24]	Left neck (tcVNS)	*Active*: 1 ms bursts of 5 kHz sine wave repeated at 25 Hz. Maximum voltage: 24 V. Maximum intensity 60 mA.	Single dose for 120s.	*N* = 30 (13 females).
Mondal, et al. [25]	Left neck (tcVNS)	Same as [24].	Two doses for 120s.	*N* = 19 (3 females).
Mondal, et al [26].	Left neck (tcVNS)	Same as [24].	Two doses for 120s, three times per day for 4 weeks.	*N* = 36 (3 females).
Farrand, et al. [97]	Left neck (iVNS)	500 ms train of 15 biphasic pulses. PW:100 μs, frequency:30 Hz every 30s, intensity:0.8 mA.	Two doses for 30 minutes per day for 10 days.	*N* = 26. All male rats. VNS initiated 11 days following last lesion or sham.
Jiang, et al. [98]	Left ear (cavum concha taVNS)	500 ms train of 15 biphasic pulses every 30s. Frequency: 30 Hz, intensity: 0.8 mA.*	One dose for 30 minutes every other day for 8 days.	*N* = 18. All male rats. VNS initiated 7 days following lesion or sham.
Farrand, et al. [95]	Left neck (iVNS)	500 ms pulse train of 15 biphasic pulses every 30s. PW:100 μs, frequency:30 Hz, intensity:0.8 mA.	Two doses for 30 minutes per day for 10 days.	*N* = 46. All male rats. VNS initiated 11 days following last lesion or sham.
Farrand, et al. [96]	Left neck (iVNS)	4 groups. Sham; Low-frequency VNS (10 Hz); high-frequency VNS (20 Hz); microburst VNS (300 Hz, 10 pulses per burst). PW:250 μs, intensity:0.75 mA for all groups.	LowVNS:30 min on 23.5 hours off; highVNS:30s on 5 min off for 24 hours per day; burstVNS:19s interburst interval for 24 hours per day.	*N* = 25. All male rats. VNS initiated 11 days following last lesion or sham.
Kin, et al. [115]	Left neck (iVNS)	5 groups. Sham; 0.1 mA; 0.25 mA; 0.5 mA; 1 mA intensity. Biphasic square pulses. PW:500 μs, frequency:30 Hz.	All groups received VNS consisting of a cycle of 30s on and 5 min off for 14 days.	*N* = 50. All female rats. VNS initiated 15-minutes following lesion or sham.

Notes: *pulse width not reported. Abbreviations: PW, pulse width. Hz, hertz, mA, milliamps. S, seconds. V, volts.

sham, although only step length variability reached significance. Both gait characteristics have been shown to be DA-treatment resistant [23,116] and potentially cholinergically mediated; thus, improvement may be due to upregulation of neurotransmission in the latter system, possibly in the cholinergic nbM or PPN regions. In both studies, stimulation was well tolerated with no adverse events reported. Finally, a very recent randomized, double-blind sham-controlled crossover trial showed that multi-dose tcVNS over 30 days improved gait velocity, step length, and step time in patients during active stimulation that was not observed following sham stimulation [26]. This study furthermore showed that active stimulation resulted in a significant improvement on the Unified Parkinson's Disease Rating Scale-III over and above that seen following sham stimulation. It is unclear, however, if any of these effects were mediated by improved cholinergic neurotransmission. Further studies would be needed to clarify this using appropriate methods. The authors of this study reported that no carry-over effects were observed following the intervention. Although no adverse effects were reported following repeated use of the device, a minority of patients withdrew from the study (both during the active and sham conditions) due to discomfort associated with the device use. Reassuringly, a large majority of participants were able to successfully carry out the stimulation at home.

All three studies conducted in people with Parkinson's employed cervical VNS devices provided by the same manufacturer. All stimulation parameters are hardcoded in the device except the current intensity which can be adjusted by the participant (Table 1). None of these studies reported the average current intensity used by participants.

In summary, tcVNS may have beneficial neuromodulatory effects on treatment-resistant gait characteristics and falls in PD. Potential putative mechanisms could be reduced neuroinflammation, reduced α-synuclein aggregation, increased neurotropic factor signaling and/or upregulated cholinergic neurotransmission. The use of a non-pharmacological adjunct to rehabilitate to improve gait in Parkinson's is an intriguing development, which merits further exploration. A larger randomized sham-controlled, multi-dose tcVNS study is currently being trialed in our group (ISRCTN19394828).

4. VNS leads to improvement across several cognitive domains

4.1. VNS and cognition in non-PD populations

Both iVNS and nVNS have been found to improve cognitive ability in animal and healthy human subjects. In early animal studies, iVNS increased memory retention in rats [117,118]. This was later replicated in epilepsy patients [119], where iVNS facilitated retention/recognition memory [120–122] and complex executive function [123,124]. Most of the nVNS literature has concentrated on utilization of taVNS [125–131], although one recent study did find improved cognitive performance using the cervical tcVNS approach [132].

There is some evidence that performance in associative memory is improved following taVNS in a group of older adults [125], perhaps attributable to NE neuromodulation. Kaan et al. [126] also found some evidence that taVNS improved memory of item order in healthy young adults.

taVNS can also enhance higher-order executive functions such as cognitive flexibility, which can be thought of as the ability to switch between different mental concepts and produce appropriate responses. Integral to this skill is inhibitory control, whereby a prior attentional focus is 'switched off' thus freeing up the capacity to attend to a new task [133]. Active taVNS improved response selection in healthy young adults, and Serial Reaction Time performance; it also enhanced inhibitory control [130]. Earlier work, however, suggested that taVNS might only assist response inhibition when the working memory load is high [127]. A more recent study by Borges and colleagues [129] found that performance on the set-shifting task, but not selective attention or response inhibition, was improved by taVNS.

VNS has additionally been explored in the context of cognitive impairment. The development of PD dementia (PDD) is a frequent and distressing complication of the disease, with a cumulative incidence approaching 80% in community-based studies [134–136]. Mild cognitive impairment in PD (PD-MCI) may be a prodromal stage of PDD and can be present in up to 40% [137]. Although enhanced cognitive function following VNS has not yet been assessed in PD/PDD, there has been some success with its use in Alzheimer's Disease (AD) [32,33,138]. An initial pilot study [32] recruited 10 AD patients who underwent iVNS over a period of 10 weeks. At the three-month follow-up, improved scores were achieved on the cognitive subset of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Mini Mental State Exam (MMSE) in 7/10 and 9/10 patients, respectively. These outcomes were mostly maintained at 6-months, with 7/10 patients still scoring higher on both scales [32]. Later, further seven AD participants were added to the sample and were followed up for 1 year [33]. Improved scores on the ADAS-cog (in 7/17 patients), and MMSE (in 12/17 patients) were sustained at 1 year after implantation. The treatment was well-tolerated, with minimal adverse effects, and no decline was reported in quality of life or mood during the study period. While this preliminary work suggests that iVNS can improve cognitive function in AD, the evidence base is minimal and limited by small participant numbers and a lack of control comparator group.

4.2. VNS in depression and anxiety

Individuals with PD are more likely than the general population to experience neuropsychiatric symptoms [139]. Depression is particularly common, and it has a substantial impact on a PD patient's ability to carry out daily activities [139–141]. Depression can predate the motor features of PD for up to several years [139], suggesting that psychiatric symptoms are also mediated by the pathophysiology of PD itself.

The management of depression in PD may include optimization of anti-Parkinson medications, the use of antidepressants [139] and psychological therapies [142]. In the general population, VNS has been used and approved for treatment-resistant depression. The scientific basis for this originated from animal studies, which established significant

anti-depressant effects of iVNS in rats [5]. In this context, the proposed underlying mechanisms of VNS include: i) changes in areas of the brain that are implicated in depression, ii) enhanced levels of NE and serotonin, and iii) increased BDNF, which may in turn decrease the neuronal loss associated with depressive disorders [71,143]. In human studies, both iVNS [144] and taVNS [145–147] have demonstrated efficacy in reducing depressive symptoms. Similarly, there is work to suggest that both iVNS and tcVNS may be beneficial in improving anxiety [30,31]. Thus far, it is unclear whether these outcomes can be achieved in PD, but there is evidence to suggest VNS can help in the management of depressive disorders and that iVNS improves quality of life in patients with epilepsy [148].

5. Other actions of VNS

VNS has been shown to improve autonomic functions. For example, VNS may modulate heart rate variability (HRV), which is inversely related to the levels of inflammatory markers, and is known to be diminished in PD [149]. It is theorized that VNS can improve autonomic function by reducing the sympathetic and enhancing the parasympathetic tone of the ANS. Furthermore, VNS may be an attractive approach to reduce fatigue and improve gastroparesis, which is also a common feature in PD [150,151].

5.1. Autonomic function

HRV refers to the beat-to-beat alterations in heart rate. Higher resting HRV is associated with good mental health and emotional well-being, whereas reduced HRV and vagus nerve activity have been associated with increased morbidity and mortality, and greater prevalence of psychiatric conditions, such as depression and anxiety [146,152].

In healthy adults, preliminary evidence suggests minimal effects of taVNS [153–156] on HRV parameters. An additional layer of complexity relates to the variable stimulation parameters used which differ somewhat between studies in addition to age groups being studied.

In healthy young and middle-aged adults taVNS with a combination of 500 μs pulse width and 10 Hz stimulation frequency, but participant-specific current intensity produced the greatest effect on heart rate relative to sham (electrodes placed on the earlobe) [153]. Another study assessed varying taVNS current intensities (0.5, 1 and 1.5 mA with other parameters held constant: 200–300 μs pulse width, 25 Hz frequency and cycle duration as 30 s on/off) on autonomic function in healthy young adults [129]. This study showed that cardiac vagal activity increased in participants relative to rest, but this increase was not related to stimulation intensity or when intensity was self-controlled versus when it was pre-set by the researchers. Moreover, statistically significant differences in cardiac vagal activity were not reached when comparing active or sham conditions.

The effects of VNS on autonomic function in aging remains elusive and requires further investigation. In one study, healthy older adults underwent continuous stimulation via the vagus using taVNS [157]. The authors showed that a single 15-min session per day for 14 days increased several measures of HRV in participants with some of these effects outlasting the period of stimulation. The authors furthermore showed that lower cardiac vagal activity at rest better predicted increased HRV under stimulation.

Lack of cardiac effects following nVNS may be due to the left side being stimulated, whereas effects may be more pronounced following right-sided stimulation [154]. Using taVNS, De Couck and colleagues [154] assessed effects of laterality (right or left cymba conchae) on measures of HRV in healthy young and middle-aged adults. This study primarily showed that right-sided stimulation resulted in increases of the standard deviation of all beat-to-beat (RR) intervals (SDNN; thought to reflect both sympathetic and parasympathetic output). A trend for similar effects was observed following left-sided stimulation.

Using taVNS, Weise and colleagues [149] studied vagal evoked potentials from the ABVN, integrity of the vagal nuclei complex and heart rate in 50 patients with PD before and during stimulation. Both the left and right tragus of the ear were stimulated (square impulses, pulse width: 0.1 ms, current intensity: 8 mA and frequency: 0.5 Hz). In this study, the authors found no differences between groups in either the latency or the amplitude of ABVN evoked potentials between groups. Furthermore, although the components of HRV were lower in PD relative to matched healthy volunteers at baseline, there was no effect of taVNS on any component [149]. It is likely however that the authors of this study [149] are recording afferent nerve volleys as opposed to cortically generated potentials. Follow-up studies are therefore warranted.

5.2. Fatigue

A recent study assessed the efficacy of tcVNS in patients with primary Sjögren's syndrome, which is an immune-mediated inflammatory condition characterized by chronic fatigue [27]. The authors instructed participants to apply stimulation sequentially to the left and right vagus nerves twice daily for 26 days. Results showed that physical fatigue, but not mental fatigue, and daytime sleepiness were reduced at the study endpoint relative to baseline, with significant reductions in certain cytokines, as discussed above [27].

5.3. Gastroparesis

Gastroparesis, or delayed gastric emptying, are common and under-recognized in PD [158], with changes in the DMNV implicated [37]. The efficacy of VNS in resolving gastroparesis has been attributed to the vagus nerve role in the genesis and maintenance of nausea and vomiting, which are two of the cardinal symptoms of gastroparesis [159]. Two studies have thus far provided some evidence of a beneficial effect of nVNS on gastroparesis in non-PD populations [28,29]. Both studies asked participants to apply tcVNS to left and right vagus nerve sequentially for a minimum of three [28] and four [29] weeks. Both studies reported reduced gastroparesis in participants as indicated by reduced scores on the Gastroparesis Cardinal Symptom Index.

6. Conclusion & future prospects

PD is a common neurological condition with a number of motor and non-motor features. Although DA loss is universal, other neurotransmitters and mechanisms are now recognized as underpinning the neurobiology of the disease. Dopaminergic treatment can improve some features, but a number of dopa-resistant characteristics are established, and alternative treatment options are required. VNS is a potential non-pharmacological intervention that has the potential to improve gait, cognition, fatigue, and autonomic function, although further work is required to establish the mechanistic foundation for PD. Potential mechanisms include augmentation of cholinergic transmission, reduction in neuroinflammation and potentiation of NE release. Multi-dose sham-controlled studies are required to determine the proof of concept and feasibility of VNS in PD.

7. Expert opinion

Prevention of falls in older people is a public health priority. Gait disorders are a primary driver of falls and are common manifestations of aging syndromes such as sarcopenia – muscle atrophy – and frailty as well as neurodegenerative diseases. With regard to the latter, PD is a specific architype; where the burden of gait impairments and falls risk is greatest. The impact of gait dysfunction and falls in PD is such that people with PD who voted for them as the number one research priority in a recent James Lind Alliance and Parkinson's UK priority setting partnership [160].

Over the past 25 years, the global burden of PD has more than doubled due to increasing numbers of older people, longer disease duration, and environmental factors; this has been associated with an increase in disability-adjusted-life-years [161]. nVNS could contribute to understanding the mechanisms of aging and treating age-related diseases such as PD, by exploring novel mechanisms and potential non-pharmacological treatments for gait disorders in PD. Targeting specific gait characteristics that underpin fall risk could conceivably reduce the morbidity and mortality associated with falls in PD, with wider implications for other aging and neurodegenerative conditions if efficacy is demonstrated. The potential benefits of a nonpharmacological, low-cost, simple-to-use, home-delivered electroceutical approach to boost cholinergic function, improve gait parameters, and reduce falls risk in this patient group are immense. If cognitive function were also be improved, as indicated in animal and healthy human studies, this would provide significant additional benefits. Importantly, because nVNS is FDA/MHRA approved for the treatment of common neurological and psychiatric disorders, obstacles to market are reduced and patient benefit may be seen much more promptly than with a novel device.

Although research in humans using nVNS is still in its infancy with research utilizing nVNS beginning around the start of this century, the number of publications and conditions utilizing nVNS are steadily increasing [10]. There are still several technical limitations or parameters that need to be assessed, including the optimal current intensity, frequency, pulse width, cycle duration, and waveform shape from the nVNS device. Even laterality could be reviewed, and studies are needed to determine if left, right or alternating left/right stimulation is superior in terms of neurotransmitter release. Additionally, studies informing the optimal number of dosages and treatment tolerance are needed. Finally, focality of nVNS has not been studied to our knowledge and studies assessing whether nVNS (and in particular tcVNS) activates other surrounding nerves are lacking. However, Yakunina and colleagues [62] showed that stimulation of the tragus and cymba conchae elicit increased BOLD response measured using fMRI in areas that are part of the vagal pathways including the NTS, whereas stimulation of the infero-posterior wall of the ear canal did not.

How the difference in stimulation parameters affects the response to the stimulation is a current hot topic (see some discussion in [10]). Both manufacturers of the most widely used commercially available nVNS devices (NEMOS® and gammaCore®) do not allow adjustment of most stimulation parameters. In both cases only the stimulation intensity can be adjusted by the user. Consequently, custom-built devices stimulating the outer ear (or direct vagal stimulation in animals) are therefore becoming increasingly prevalent. In people with Parkinson's varying stimulation parameters of nVNS devices have not been assessed. Regarding the studies in PD animal models, the critical question of whether these findings can be translated into human patients remains to be answered. Another issue that needs to be disentangled is the effects of nVNS as an adjunct treatment in patients on acetylcholinesterase inhibitors.

Advanced neuroimaging methods such as functional near-infrared spectroscopy and wearable neuroimaging technology employing magnetoencephalography [162] may be used to investigate nVNS underlying mechanisms. Also, nVNS effects on the enteric nervous system, neuropsychological functioning and motor control are currently unclear in humans. Nonetheless, preliminary data from three studies in humans [24–26] have already provided convincing evidence that tcVNS can improve dopaminergic treatment-resistant gait characteristics in early-stage PD, but it is currently unclear if these effects are sustained when participants no longer stimulate themselves. Finally, health economic data would be beneficial to collect, to determine costs and potential savings in relation to other treatments [1]. To date, there are no head-to-head studies of iVNS vs. nVNS, although inherently invasive in nature, potential adverse events and presumed greater costings would favor nVNS.

Finally, a brief discussion on the use of sham stimulation in VNS is merited. When using other neuromodulation techniques such as transcranial magnetic or current stimulation (TMS, tCS) the use of sham stimulation is common and is thought to provide an adequate control condition [163]. However, providing such a control condition is not without its challenges. The TMS coil makes an audible clicking sound when the magnetic pulse is delivered to the scalp followed by some scalp irritation as well as noticeable contraction of some muscles. Consequently, its use as a control condition, by definition, has been criticized [164].

Similar issues are faced when using tCS where the stimulation produces noticeable and often painful sensory perceptions. The most common approach to sham tCS is to ramp the device up to a predetermined intensity before ramping the current down after a few seconds [163]. Nonetheless, these sensory perceptions are substantially more noticeable and frequent during active tCS relative to sham [165] which throw into question its use as a proper control condition in clinical research, especially in randomized controlled crossover trials. Stimulating the vagus nerve may be no different since vagal stimulation can elicit a range of side effects as noted previously [13,14]. Using taVNS it is common to place the stimulating electrodes on the earlobes of participants to not activate fibers of the ABVN. This again may cause issues in studies adopting a crossover design. Related to this gammaCore® sham devices do deliver perceptible electrical stimulation to the skin, but the frequency of pulses is low (0.1 Hz) [26], and this purportedly does not activate vagal fibers and consequently regions of the vagal pathways (i.e. NTS, LC). To that end, the sham stimulation may be considered as a limitation of the technique, making it difficult to blind participants who may be aware of the most common side effects of nVNS. However, as with TMS and tCS, this is the best option we currently have.

In summary, nVNS is an evolving technique with potential applications in a number of symptoms and conditions. Further research to delineate the exact underpinning mechanisms of action, feasibility, and to generate pilot data are required; some of which we hope will be answered in the ISCRTN registered study (ISRCTN19394828).

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