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Ultrasonographically measured atrophy of vagus nerve in Parkinson's Disease: clinical and pathogenetic insights plus systematic review and meta-analysis

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ABSTRACT

Introduction. According to the current Parkinson's Disease (PD) pathogenesis hypotheses, the vagus nerve (VN) is essential for disease development. It has been identified as a main entry point for misfolded α-synuclein to the central nervous system, and surgical vagotomy appears to limit disease progress both in animal models and in humans. A recent approach tried to assess VN size in PD patients via neck ultrasonography, but the clinical value of this method is yet to be established.

State of the art. A systematic search of the MEDLINE, Scopus, and Web of Science databases was conducted, and 12 case-control studies were included. Meta-analysis revealed a modest reduction in VN size in PD (effect size — 0.79 SD (95%CI [–1.34, –0.25] p = 0.004)). The atrophy was more pronounced on the right side, and the nerve was smaller in females. In PD patients, VN reduction correlated with cardiac parasympathetic function decline and with advances in motor ratings. The discrimination potential for PD diagnosis, and any association with other non-motor domains, remains unclear.

Clinical implications. VN atrophy in PD could be detected by ultrasound imaging. However, the clinical significance of this phenomenon has yet to be clarified. Size reduction is not readily apparent and is individually variable. However, it may be considered a promising means to improve early PD diagnosis and the recognition of autonomic dysfunction.

Future directions. With more extensive research, VN sonography could provide useful evidence regarding disease origins. Imaging should be performed together with a profound clinical assessment and biomarker testing to establish the role to be played by this method in future practice.

Keywords: Parkinson's Disease, movement disorders, neurodegenerative diseases, ultrasonography, ultrasound, vagus nerve

Introduction

The vagus nerve (VN) has recently become an important focus in Parkinson's Disease (PD) research. The longest of the cranial nerves provides predominantly visceral sensory information from the gastrointestinal, respiratory, and cardiac systems, while efferent fibres supply internal organs with parasympathetic innervation. According to Braak's hypothesis of PD origins, VN becomes an entry to the central nervous system for alpha-synuclein (α-syn) pathology [1]. Despite recent opinions that this ascending pattern of pathological process does not represent all cases [2, 3], the experimental evidence supporting the concept of vagus vulnerability is growing. In animal models of the disease, misfolded α-syn spreads through the VN to the brainstem, as well as in the opposite direction [4-6]. In humans, essential supportive data comes from large epidemiological studies which have shown that surgical vagotomy is associated with a reduced risk of developing PD in subsequent years [7, 8]. This effect occurred for a non-selective vagotomy procedure, and the risk decreased more the earlier the operation was performed, supporting the hypothesis of progressive VN transmission.

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Recently, researchers have been trying to assess VN affection in PD *in vivo* using high-frequency ultrasound. It has been assumed that transmission of α-syn induces a degenerative process, resulting in the possibility of identifying atrophy of VN. However, previous papers provided contradictory results, and it remains unclear whether, and if so by how much, the nerve is reduced in patients.

The purpose of this review was to summarise the most recent data on VN ultrasonography in PD to provide insights into disease pathogenesis, its clinical correlations, and the possible diagnostic utility of this method.

Methods

Search strategy

We conducted a systematic review of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. A search was performed to find publications released up to October 2023 using PubMed, Web of Science, and Scopus. These databases were interrogated using the following words: "Parkinson's Disease", "vagus nerve", "sonography", "ultrasound", and "ultrasonography". A query for each database was constructed with an appropriate advanced search creator and according to the general order as follows: "Parkinson's Disease" AND "vagus nerve" AND (ultrasound OR sonography OR ultrasonography OR sonograph* OR ultrasonograph*). An additional screening through the references of included research was carried out.

Eligibility criteria

Studies were considered for inclusion in this review if they met the following criteria: (1) it was an original study on human participants; (2) it was written in English; (3) the participants were diagnosed clinically with idiopathic PD; and (4) if it described an ultrasonographical examination of the VN. We excluded studies that: (1) did not report the mean VN area; or (2) reported parameters other than the cross-sectional area.

Study selection and data extraction

Abstracts were screened and full texts were assessed for inclusion by a single investigator. Appropriate studies proceeded to data extraction, which was focused on patients and control criteria, ultrasound examination, disease severity scores, and non-motor symptoms evaluation. The investigated outcomes were the mean left and right VN cross-sectional area (CSA). Additional clinical correlates and variables were obtained if they were being investigated by the authors.

Quality assessment and risk of bias

The quality of the studies and the risk of bias were assessed by a single reviewer using the QUADAS 2 tool [10]. This questionnaire includes a comparison of the index test to the reference standard method, so the reference standard was considered as the established clinical criterion for PD diagnosis, since there is no standard method for vagus nerve imaging other than sonography.

Statistical analysis

For each included study, mean CSA of the right and left vagus nerve were exported with standard deviations. For values reported as median and interquartile range, values were transformed according to the previously described estimation method [11]. Effect size and standard error using Cohen's *d* were calculated using the Campbell Collaboration calculator [12]. Every test was run for both variables separately as well as for the bilateral pooled area. Statistical calculations and graphs were made using JASP (v. 0.17.3) computer software.

Meta-analysis was performed by adopting a random effects model with a restricted maximum likelihood method. Subsequently, subgroup analysis and meta-regression were tested to identify the sources of heterogeneity. We checked for influence factors such as the controls' clinical condition, precision of vagus nerve measurement, mean disease duration, mean UPDRS III score, and mean non-motor symptoms score. Sensitivity analysis, aimed at addressing possible arbitrary decision bias, was performed.

Results

Included research

The total number of included studies and the reasons for exclusion are set out in Figure 1. Of 18 relevant articles, three were identified as conference abstracts covering the same research as subsequently published papers [13–15]. One study measured only the diagonal diameter of the vagus nerve [16] and another did not report CSA values directly [17]. One abstract consisted of a joint experimental group of PD and atypical parkinsonism [18].

All studies were observational in design, and compared ultrasonographically measured vagus nerve between PD patients and non-parkinsonian controls.

Regarding experimental group recruitment, most studies (n = 7) adopted Queen Square Brain Bank criteria for diagnosis of PD. Control groups mostly consisted of healthy participants (n = 7), patients without neurodegenerative disease (n = 2), or a mix of these groups (n = 2). Of the studies included in the meta-analysis, two contained two separate control groups [14, 19]. In these cases, only disease-free controls and age-matched controls respectively were included in the meta-analysis. A quality assessment and the risk of bias of the studies are set out in Figure 1.

Systematic review

Population and outcomes

Overall, our analysis included 458 PD patients and 383 controls. The mean age of patients was 68.8, the majority were male (52%), and average disease duration was 7.7 years.

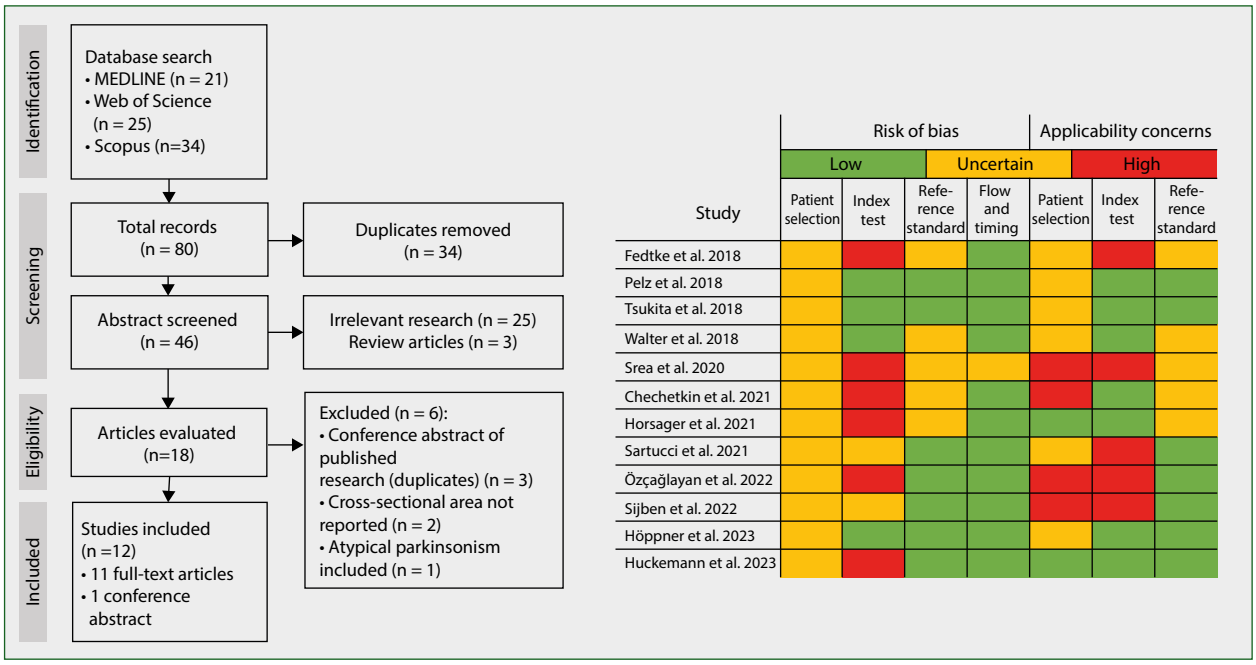

Figure 1. Flowchart of study identification and selection (left), and quality and risk of bias assessment of included studies (right)

The mean Hoehn and Yahr (H&Y) stage of participants (eight studies) was 2.5 and the mean Unified Parkinson's Disease Rating Scale (UPDRS) part III score (nine studies) was 26. SCOPA-AUT (three studies) was rated at 14 on average.

10/12 studies reported a significant reduction of VN CSA in the PD group. The age of participants in each study was generally homogenous, and in almost all studies there was no correlation between VN CSA and age. It also did not differ between patients aged below and above 65 in a single study [20]. However, when controls were significantly younger, the nerve size decreased with age [14]. The VN was also smaller in females, which required sex adjustment in one study [21, 22]. The influence of body mass index (BMI) on measurements was negligible [15, 21]. In all studies except for one, the right vagus nerve was larger than the left, regardless of disease status [14].

Disease duration varied across studies, but we found no robust association between VN and the time since onset [13–15, 20, 22, 23]. Even in newly diagnosed patients, a reduction of VN was visible [21]. Nonetheless, the VN CSA did correlate with the UPDRS score, showing its connotation to motor impairment [14, 20, 22, 24]. VN was also associated with increased bradykinesia and tremor score of UPDRS [19, 24]. Only three studies classified patients according to disease subtype, and a single report described greater reduction of the VN in the akinetic-rigid subtype than in the mixed one [14, 19, 25].

Ultrasound examination

All studies used similar ultrasound equipment with linear, high-frequency probes. Six teams measured VN at the level of the thyroid, while three groups did it higher up, near the carotid bulb. The precision of scans differed substantially between authors, ranging from 0.01 mm^2 to 1 mm^2 in some studies. There were two approaches to the measurement of CSA. The first, more popular, one was based on tracing within the inner side of the hyperechoic epineural rim with automatic calculation of the area. The other approach measured the distance of the long (*a*) and short (*b*) axis inside the epineurium and calculated the area using the $a*b*\pi/4$ formula [14]. A study comparing both methods found no significant difference between them [26]. It is worth noting that both approaches might be applied online (during the examination using ultrasound machine software) or offline (after image export to external software).

Non-motor symptoms

Different approaches were used to assess the burden of non-motor and autonomic symptoms, but only three studies used the SCOPA-AUT questionnaire ranking the severity of autonomic dysfunction [13, 26, 27]. Another three articles described a correlation between VN size and PD-NMSQ score, which is a screening tool for various non-motor symptoms [14, 20, 22].

Extended cardiac function examination was mentioned in three papers [14, 22, 27], of which two reported a correlation between VN CSA and parasympathetic heart rate variability parameters in rest and tilt table examinations [14, 27]. Two studies described a correlation between VN area and gastrointestinal symptoms reported in non-motor symptoms scales [13, 20]. Nevertheless, it was not confirmed by changes in colonic transit time, nor colon acetylcholinesterase density [21].

Of three studies that tested cognitive performance, one reported a relationship with right VN size [22]. Detailed associations between VN CSA and non-motor symptoms are set out in Table 1.

Table 1. Main characteristics of included studies

Study	Sample	Level of measurement	Precision of measurement (mm2)	Mean disease duration (years)	Mean UPDRS III	VN reduction in PD	Signs and symptoms associated with VN reduction				
							Associated motor performance	Associated non-motor symptoms	Association with cardiovascular performance	Association with gastrointestinal symptoms	Association with cognitive performance
Fedtke et al. 2018 [19]	32 PD 30 C*	N/R	1	N/R	33	No	Bradykinesia score No correlation with H&Y, and tremor/PIGD index	N/R	N/R	No correlation with reported constipation	N/R
Pelz et al. 2018 [23]	35 PD 35 C	Thyroid	0.1	10.6	22.8	Yes	No correlation with UPDRS and H&Y	No correlation with NMSQ	N/R	No correlation with gastrointestinal domain of NMSQ	No correlation with MoCA
Tsukita et al. 2018 [13]	21 PD 21 C	Carotid bulb	0.01	5	18.3	Yes	H&Y** No correlation with UPDRS	No correlation with total SCOPA-AUT	No correlation with cardiovascular SCOPA-AUT	Gastrointestinal SCOPA-AUT**	No correlation with MMSE
Walter et al. 2018 [14]	20 PD 61 C*	Thyroid	0.01	10.1	30.7	Yes	UPDRS III	Total NMSQ, autonomic score of NMSQ	Heart Rate Variability (RMSSD)	N/R	N/R
Srea et al. 2020 [24]	32 PD 25C	N/R	N/R	N/R	N/R	Yes	UPDRS III, bradykinesia score, and tremor score No association with substantia nigra echogenicity	No correlation with NMSS	N/R	N/R	No correlation with MoCA
Chechetkin et al. 2021 [25]	32 PD 32 C	Carotid bulb	0.1	4.33	37	Yes	Akinetic-rigid type and substantia nigra hyperechogenicity No correlation with UPDRS	No correlation with NMSQ	N/R	N/R	N/R
Horsager et al. 2021 [21]	63 PD 56 C	Thyroid	0.01	0.66	23	Yes (after sex adjustment)	No correlation with H&Y	N/R	N/R	No correlation with colonic transit time, and colon acetylocholinesterase density	N/R
Sartucci et al. 2021 [15]	20 PD 20 C	Thyroid	1	10.1	N/R	Yes	No correlation with H&Y	N/R	N/R	N/R	N/R
Özçağlayan et al. 2022 [20]	43 PD 44 C	Thyroid	1	6.6	22.2	Yes	UPDRS III	NMSQ	N/R	Gastrointestinal NMSQ score	N/R
Sijben et al. 2022 [26]	31 PD 51 C	N/R	N/R	7.9	N/R	No	N/R	No association with SCOPA-AUT	N/R	N/R	N/R
Höppner et al. 2023 [22]	49 PD 24 C	Thyroid	0.1	6.4	20.6	Yes	Total UPDRS UPDRS III	NMSQ	N/R	No correlation	Right VN correlated with MoCA
Huckemann et al. 2023 [27]	87 PD 40 C	Carotid bulb	0.01	6	30	Yes	N/R	N/R	Parasympathetic HRV parameters at rest and after tilting	N/R	N/R

N/R — not reported; H&Y — Hoehn and Yahr stage; UPDRS — Unified Parkinson's Disease Rating Scale; NMSQ — Non-motor Symptoms Questionnaire; NMSS — Non-motor Symptoms Scale; SCOPA-AUT — Scales for Outcomes in Parkinson's Disease — Autonomic Dysfunction; RMSSD — root mean square of successive differences; MoCA — Montreal Cognitive Assessment; MMSE — Mini-Mental State Examination; *in study by Fedtke et al., control group consisted of 15 healthy controls and 15 disease controls (6 with stroke, 7 essential tremor, 2 headache); Walter et al. reported 61 controls, of whom 21 were age-matched; ** authors described results at level of statistical tendency ($0.05 < p < 0.1$)

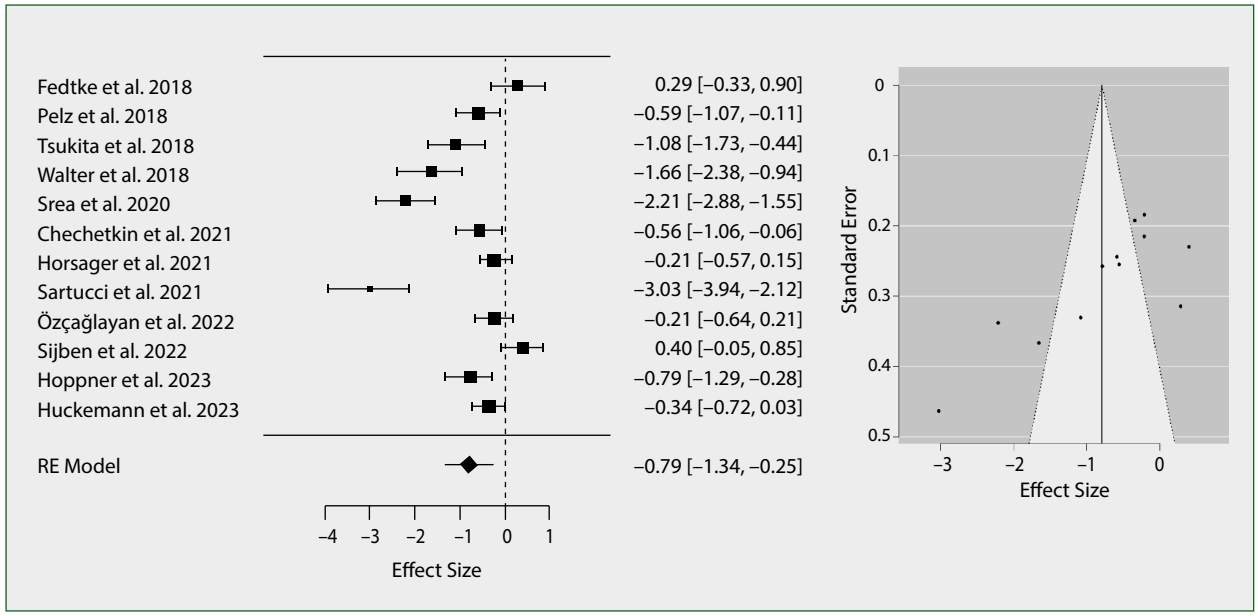

Figure 2. Forest plot of meta-analysis. Effect sizes represent a difference in bilateral mean vagus nerve cross-sectional area between Parkinson's Disease patients and controls expressed in standard deviation units (ES = 1 means difference between groups equal to 1 standard deviation). Values below 0 indicate reduced vagus nerve in parkinsonian patients. Funnel plot (right) may suggest possible publication bias

Meta-analysis

Performed meta-analysis revealed that pooled effect size was −0.84 (95%CI [−1.44; −0.25], p = 0.005) for the right VN and −0.74 (95%CI [−1.24; −0.23] p = 0.004) for the left. The effect size for a bilateral mean of the VNs was equal to −0.79 (95%CI [−1.34, −0.25] p = 0.004). The effect size of each study is presented as a forest plot in Figure 2.

Sensitivity analysis and heterogeneity

Sensitivity analysis was done to explore the impact of our selection system on the meta-analysis results. It revealed that inclusion of all the controls in the studies by Walter et al. [14] and Fedtke et al. [19] would not change the results noticeably. If we considered only articles published in peer-reviewed journals (and this means without a single conference abstract [24]) the results would mildly weaken (bilateral effect size −0.66 95%CI [−1.18; −0.14], p = 0.013). Furthermore, we identified three studies as outliers [15, 24, 26], which were excluded in the next step of analysis. As a result, the effect size for bilateral mean VN decreased to −0.54 (95%CI [−0.85; −0.22], p < 0.001). A cross-validation (the 'leave-one-out' method) indicated that no single study significantly influenced the results.

Our meta-analysis showed substantial residual heterogeneity of studies (I^2 = 93%). Applied meta-regression did not identify any sources of heterogeneity. Explanatory subgroup analyses showed that lower effect size and non-significant heterogeneity were attributed to subgroups of studies including patients with disease duration of less than seven years (n = 6 studies). The funnel plot was asymmetric (Egger's test p < 0.001), which implies possible publication bias.

Discussion

Vagus nerve atrophy

The current evidence suggests atrophy of the vagus nerve in PD which can be detected by ultrasound examination. On a transverse scan, VN presents as a hypoechogenic structure within the cervical sheath with an average cross-sectional area of 2.4 mm^2 for healthy controls and a 16% reduction observed in PD patients (Fig. 3).

The slight atrophy is probably due to specific nerve structure, since axons make up only 40% of the nerve area [28]. In a cervical portion of VN, there are c.5 times more unmyelinated than myelinated fibres, but in terms of spatial distribution on cross-sections, myelinated and unmyelinated fibres occupy comparable areas [29]. In general, thin unmyelinated C-fibres bring visceral sensory connections to the solitary nucleus, while medium-sized B-fibres beginning from the dorsal nucleus of vagus (DMV) are responsible mainly for parasympathetic function [30]. These connections are believed to be prone to degeneration, because α-syn has been found in the brainstem nuclei with apparent prediction to DMV [31]. This stands in contrast to sensorimotor A-fibres

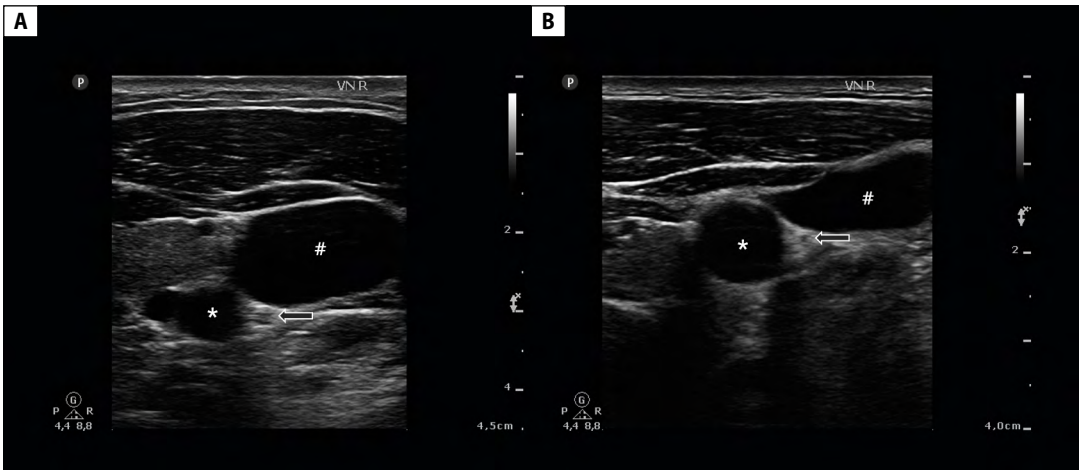

Figure 3. Example VN ultrasound images of two individuals (authors' own material): **A** — subject without neurodegenerative disease (58-year-old male), VN CSA 3.4 mm^2; **B** — patient with advanced PD (65-year-old male, disease duration 11 years, H&Y stage 4), VN CSA 1.6 mm^2. Outlined arrow — vagus nerve; * — common carotid artery; # — internal jugular vein; VN — vagus nerve; CSA — cross-sectional area; H&Y — Hoehn & Yahr stage

of the nucleus ambiguus that remain spared until late disease presenting with dysphagia [31–33]. Essential data comes from the observation of VN changes in animal models of the disease [34]. Interestingly, phosphorylated α-syn was concentrated not in axons as one would expect, but predominantly in Schwann cells (SCs). The myelin sheaths were disrupted, and nerve conduction velocity was reduced, although axonal loss affected mainly B- and C-fibres. A possible mechanism is an affection of non-myelinating SCs that support thin unmyelinated fibres in Remak bundles and are crucial for their survival [29, 35]. Supporting this idea is the fact that α -syn pathology in SCs has been observed to induce cell death through inflammatory response and Toll-like receptors activation, which resulted in clinical autonomic dysfunction [34, 36]. This implies that there is primary damage to the nerve revealed by this imaging method, although descending pathology directly affecting nuclei, and causing secondary VN lesions, cannot be excluded.

VN presents with significant asymmetry; generally, right VN is larger and contains more fascicles [28]. Our meta-analysis shows that indeed atrophy is more pronounced on the right side, which indicates that ultrasound measurements are directly connected to axonal atrophy. Asymmetry of the cervical portion is associated with differences in the heart's autonomic system as the right VN innervates the sinoatrial node and the left VN - atrioventricular node. However, on the lower levels, fibres mix into a common plexus and any particular laterality is no longer present (Fig. 4) [37].

Role of vagus nerve atrophy in latest disease pathogenesis models

If we consider that α-syn passing through VN initiates nerve atrophy in the manner described before, the recognisable decreases in nerve size and conduction velocity would support the hypothesis of rostral α-syn spread in PD. A more recent concept (described as the *body-first versus brain-first* model) emphasises the existence of two distinct pathogenetic patterns [3]. According to this postulate, the ascending pattern occurs only in some patients (the so-called *body-first* type), while in others, entirely opposite dispersion through the olfactory bulb and limbic system to the substantia nigra may be found (the *brain-first* type). These distinct pathogenetic subtypes should differ phenotypically, because *body-first* patients would present with long gastric prodrome, early-occurring REM-sleep behaviour disorder (RBD), and more pronounced autonomic affection with prompt heart denervation. Presentation at an older age and more symmetric parkinsonism may be expected in these patients due to the long prodromal route and common mixing of subdiaphragmatic contralateral fibres of the VN.

On the other hand, the *brain-first* group would have presented as more asymmetric motor-predominant form, affecting younger patients with a lower dementia risk and lately presenting with sleep and autonomic disorders [3].

It is particularly challenging to identify affected individuals in the prodromal stage and test them to observe the α-syn range. One postulate is that polysomnography-detected RBD in the moment of clinical diagnosis could be a marker of the *body-first* form [38]. But other authors have found RBD to be capable of differentiating these types despite its temporal sequence [39]. Unfortunately, none of authors investigated the presence of RBD in VN sonographic studies. It has to be pointed out that for other structures, it might take several years from the initiation of cell degeneration to establish its clinical significance in a similar way like for the substantia nigra. This interval may also vary depending on unique cell susceptibility [40]. Therefore, the sequence of emerging symptoms may not fully represent the sequence of spread.

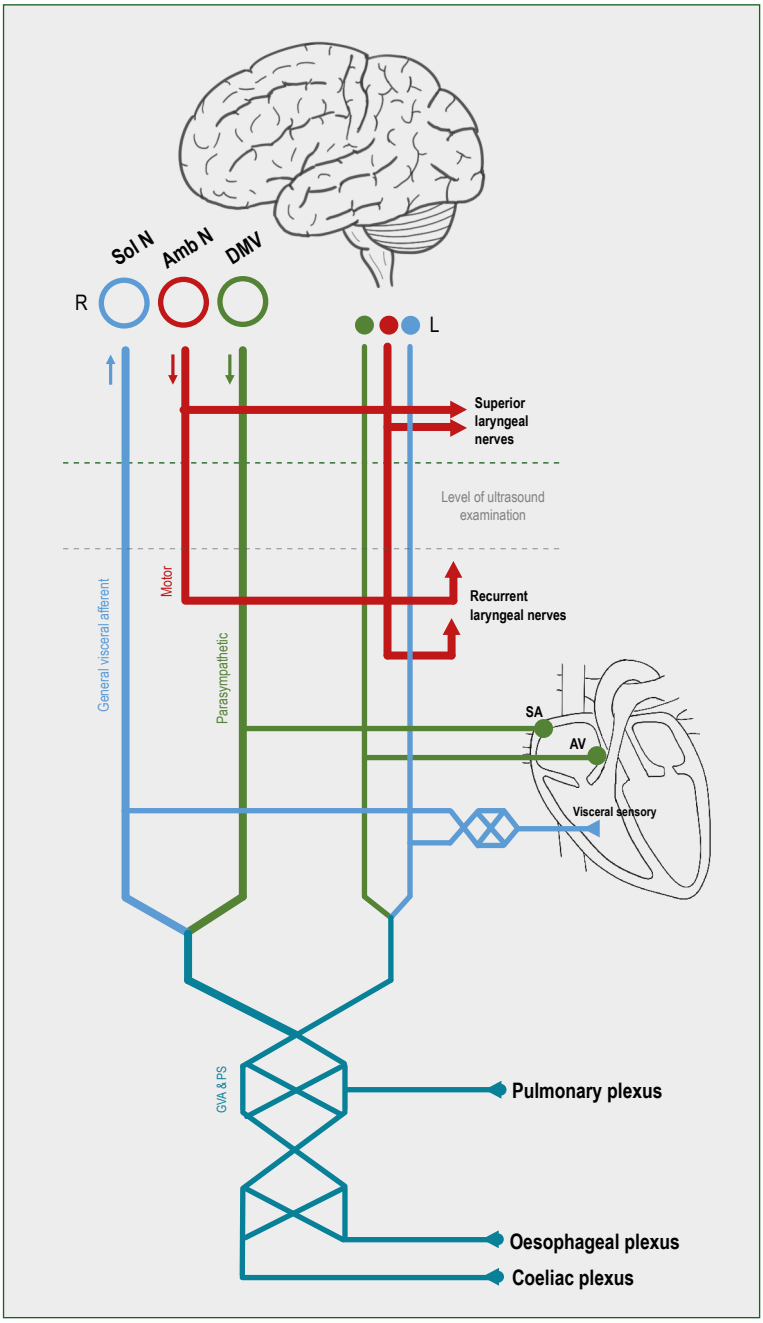

Figure 4. Schematic morphology of vagus nerve showing groups of fibres and corresponding nuclei. Significant mixing of contralateral fibres can be found at level of cardiac plexus (sensory fibres), pulmonary plexus (sensory and autonomic), as well as oesophageal and coeliac plexuses (sensory and autonomic). Note marked level of insonation (both thyroid and bifurcation). Sol N — solitary nucleus; Amb N — nucleus ambiguus; DMV — dorsal motor nucleus of vagus; GVA — general visceral afferents; PS — parasympathetic; SA — sinoatrial node; AV — atroventricular node

However, a steep gradient of α-syn burden has been observed, and pathology seems to concentrate either in the brainstem or in the limbic system [41]. This has been incorporated in the improved α-Synuclein Origin site and Connectome (SOC) model. [42]. The *brain-first* vs. *body-first* dichotomy has been supported by several imaging modalities, but not yet by VN sonography [38, 43, 44]. Moreover, similar conclusions from post mortem studies are missing. Despite numerous animal studies indicating VN's capability of transporting α-syn, data regarding humans is scarce [4, 5]. The described absence of α-syn in VN prior to brain deposits does not support prodromal spread from the gastrointestinal system [45]. On the other hand, immunohistochemistry might not be sensitive enough to identify early changes, as pathological α-syn probably spreads

quickly in low amounts (as seeds) and initiates prion-like aggregation in vulnerable structures over many years [42, 46]. Discovering the molecular principles of α-syn's cell-to-cell spread is fundamental for a proper understanding of this field. Regarding the rostral route, the enteroendocrine cells in the gastrointestinal tract have been hypothesised to be a starting point. These α-syn-expressing cells are exposed to exogenous factors in the intestinal lumen, and connect closely with enteric neurons [47]. However, the number of α-syn positive enteric neurons is much lower than the number rich in α-syn vagal fibres [48]. The missing link that would explain mucosal to nervous transfer may be proximity transmission and neuronal uptake of fibrils depending on Ca^{2+}-calmodulin-calcineurin signalling [49, 50].

Another challenge is the mechanism in which VN is affected. As discussed, studies imply that VN is directly affected by α-syn depositions, predominantly in SCs. However, it is possible that degeneration of VN happens long after α-syn is seeded through axonal transport to the brainstem. In animal models, transport to the CNS is fast (compared to the proposed dozen years in humans) and has been detected by positive seed amplification assays [6]. However, it happens only in the presence of native non-aggregated α-syn, because α-syn-deficient mice do not develop the disease [4]. Importantly, vagotomy seems to restrict pathology by the reduction of a-syn concentration in the nerve endings. Therefore, it needs to be applied before the process is transmitted to the VN [48]. For now, the molecular mechanism of VN affection needs to be investigated, as this structure may be of particular interest for disease-modified therapies for some groups of patients at least.

After the VN, the olfactory bulb (OB) has been identified as possibly the second most important entry point to the central nervous system, and has been mentioned as a starting point of the *brain-first* subtype [51]. But the presence of Lewy bodies in the OB surprisingly often coexists with proposed brainstem-predominant (*body-first*) pathological dispersion, which has led to the emergence of the 'dual-hit' hypothesis [1].

Counterintuitively, hyposmia is a common finding in PD and it is also very frequently found in isolated RBD, a supposed prodrome of the *body-first* type [52]. Evaluation of pathological studies has reported that the OB is rarely involved in early *body-first* cases [51]. A long prodrome raises the possibility of the OB eventually becoming affected over this period. A small study using seed amplification assay in samples collected from skin biopsies and the nasal cavity seems to support the existence of two separate routes of spread, with eventual affection of the OB in *body-first* cases [53]. Hopefully, novel methods of detecting α-syn pathology would bring greater clarity to this process.

Nevertheless, we must underline that PD is a highly heterogenous disease, and even these extensive hypotheses do not explain the wide variation of clinical findings. Many different cases do not follow the typical image of PD, such as LRRK2-mutation carriers without hyposmia but with negative seed amplification assays [54]. Therefore, the evidence for vagus nerve atrophy is significant for understanding PD pathogenesis, although this should be further investigated with more detailed clinical phenotyping, and preferably compared to nuclear imaging or synuclein-detecting assays.

Significance for PD clinical evaluation

Currently, high-frequency ultrasonography is considered the gold standard for imaging shallow structures such as the nerves of the neck region [55]. There are also high levels of agreement between sonography and histopathology [28]. Overall, there is now enough evidence for the reliability of this method in the case of degenerated nerves. Nevertheless, the reduction in VN in PD patients is very subtle when compared to healthy controls. Our review estimated this reduction at around 0.4 mm^2, with the average VN of a healthy individual at 2.4 mm^2. Moreover, high interpersonal variability of VN diameter has been described, which may result from differences in age, sex, body mass, comorbid conditions, and the side being measured. This might contribute to nonsignificant results in some studies because some populations were not equally distributed in terms of sex and cardiac comorbidities [21, 26].

Considering the above, not to mention diversity across scans and examiners, the possibility of improving clinical diagnosis of PD by ultrasonographic evaluation becomes seriously diminished. Even so, the optimal method of differentiating patients from controls using VN scans is yet to be defined. Right VN shows more advanced atrophy, and therefore could be tested alone in a clinical practice setting. Another approach may be to consider the VN cross-sectional area in relation to different biomarkers, e.g. the substantia nigra hyperechogenicity area, to calculate some sort of index improving its discrimination potential. Searching for VN atrophy across atypical parkinsonism is promising and should be investigated. Early data suggests that patients with multiple system atrophy present an even more pronounced reduction in VN size than do PD patients [56].

Our post hoc analysis suggests that those studies in which the disease lasted 7+ years revealed a greater VN reduction (data not presented). However, no single study found a direct correlation between VN size and disease duration. Moreover, four studies reported a correlation between VN shrinkage and UPDRS III score [14, 20, 22, 24]. This might hint that VN atrophy progresses not with PD duration, but rather with disease severity and motor symptom advance, although no follow-up data has been published to date. Also, UPDRS does not exactly reflect disease progression, given that it is somewhat subjective and dependent on the patient's temporary condition during the examination [57]. Bradykinesia score has been mentioned as correlating negatively with VN area, and a single study reported a link to the akinetic-rigid subtype [19, 24, 25]. However, disease subtyping has rarely been applied,

and on an occasion when it was the researchers did not provide a proper sample for each group [25]. Therefore, these findings should be considered as a correlation with overall symptom severity, rather than with a particular disease phenotype. For clinical applicability, it is crucial to determine how VN atrophy progresses with PD course, and how early it can be recognised. To date, only one study has included early PD patients, and in that case the decrease in VN size was already noticeable [21].

Another issue that must be addressed is the high diversity in PD that may affect the measurements. As mentioned earlier, pathogenetic duality implies that in the adopted model only *body-first* patients would present with VN atrophy, and that therefore a true effect size might be underestimated. Likewise, VN size has repeatedly been correlated with motor burden, but never with disease duration. This indicates that non-severely affected patients (presumably tremor-predominant or again *brain-first*) might not present a significant reduction in VN CSA. Therefore, it seems reasonable that VN atrophy should be explored with respect to other yet-to-be reported PD symptoms such as RBD, hyposmia or diffuse malignant subtype in general [58].

A wide association with non-motor symptoms is to be expected, as VN is a crucial part of the autonomic system. This has often been reported by authors when measured by general non-motor symptom scales. However, it is not so evident regarding particular symptom domains. The most proven connection is between the VN area and parasympathetic dysfunction measured by electrocardiography in rest and head-up tilt tests [27]. This study contained the most detailed examination of the cardiovascular system in a large sample, making the results the most reliable. A simplified method, heart rate variability (HRV) at rest, detected consistent findings in one study [59]. Decreased HRV is common in PD patients, and is especially pronounced in parasympathetic, vagal-mediated parameters such as root mean square of successive differences (RMSSD), and high frequency (HF) power [60]. Therefore, we speculate that reduced VN size may act as a morphological marker of parasympathetic dysfunction in PD.

Contradictory conclusions have been found in the context of gastrointestinal symptoms. Some correlation seems to exist between the VN area and self-reported gastrointestinal burden [13, 20]. But objective evaluation by imaging methods did not support those reports [21]. Similarly, not enough data has been presented to establish a clear association with cognitive decline.

A promising application of VN sonography would be to test whether nerve reduction could predict the future course of the disease. However, the only evident association seen to date is with heart parasympathetic performance. The first signs of autonomic dysfunction can be found already in the prodromal stage, and is an encouraging target for early diagnosis of PD [61]. Moreover, parasympathetic dysfunction seems to progress with disease duration, but not necessarily together with sympathetic denervation, which starts earlier [60, 62, 63]. Perhaps combining HRV with VN ultrasound (imaging of the parasympathetic system) and ^{123}I-MIBG cardiac scintigraphy (a biomarker of sympathetic denervation) could give further insights into structural changes of the autonomic nervous system in PD. Such an early imaging possibility would enable recognition of a subgroup of patients developing autonomic failure, related to a more malignant disease subtype. A link between HRV and dysautonomia has been described as early as in idiopathic RBD patients [64]. For now, assessing the risk of phenoconversion in this condition remains controversial due to the lack of disease-modifying therapies [65]. Likewise, autonomic dysfunction is one of the most debilitating elements of PD, and only supportive care is available today [66]. Once novel therapies start to emerge, such diagnostic tools will be essential, presumably with a special focus on subtyping biomarkers affecting treatment decisions [67].

At the moment, VN imaging, preferably in combination with VN electrophysiology (HRV), might be useful for early diagnosis of PD-related cardiovascular autonomic failure. Other motor and non-motor domains still require more extensive research.

Limitations and credibility

The results of this meta-analysis depict a decrease of VN in PD, but the notable heterogeneity of the included studies and any possible bias must be addressed. Research has differed regarding applied methods and received outcomes, and some authors have provided outlier values. However, sensitivity and subgroup analyses show that a subtle reduction of VN is consistent across previous research. Moreover, recently published larger studies align with the estimated pooled effect size [21, 27]. All analysed research brings some limitations expected for specific study designs and populations. Inclusion criteria, patient recruitment, and the clinical criteria for PD were comparable, but mean PD duration ranged from several months to 10+ years. If nerve degradation is continuous and progressive, as can be expected, it may explain some part of the variation in VN area across studies. Unfortunately, only a few authors did include information about disease subtypes in their protocols [14, 19, 25]. Additionally, non-motor symptoms were often assessed by different scales, electrophysiological or radiological measures [14, 21, 22, 27].

According to the above-described pathogenetic considerations, an observed reduction should differ between patients with primary (*body-first* PD) as opposed to secondary (*brain-first* PD) VN degeneration, or between clinical subtypes [58].

Another possible confounder is the presence of different systemic diseases that could interfere with nerve structure. It is known that a larger VN detected on ultrasound is associated with diabetes [68, 69] and chronic inflammatory demyelinating polyneuropathy (CIDP) [27, 68], while atrophy happens in

amyotrophic lateral sclerosis (ALS) [70, 71] and can be found in atrial fibrillation [72]. However, these concerns seem negligible since the presence of diabetes and neurodegenerative diseases served to exclude such individuals from the majority of studies. Some authors have attempted to exclude peripheral neuropathy in patients, and there were no differences in the diameter of peripheral nerves [15, 22], cervical nerves [14], nor in neuropathy signs. [23]

In patients treated for PD, nerve damage may be also attributed to dopaminergic substitution therapy due to increased homocysteine levels and its neural toxicity [73, 74]. Levodopa-induced polyneuropathy is a not uncommon complication of oral and intestinal treatment [75, 76]. The intestinal form, as used in advanced PD, is more often associated with acute polyneuropathy due to a possible autoimmune component [76, 77]. On the other hand, oral levodopa is a fundamental drug used in almost every PD patient for many years, and may contribute to chronic nerve damage [75]. Theoretically speaking, the neurotoxic effect of homocysteine and persistent vitamin B-12 deficiency might be to some extent responsible for observed VN degeneration. Nevertheless, the authors did not find that VN size correlated with levodopa dose [14, 15, 22]. Also, due to very early electrophysiological changes and pathological findings in the VN described earlier in this article, it is unlikely that vagal atrophy is solely caused by levodopa toxicity. However, some accelerative effect on degenerative processes inside nerves cannot be ruled out, pending a fuller investigation.

Furthermore, the precision of measurements is a critical issue when comparing studies. Probably a pooled group effect of nerve reduction may even be visible to some extent with 1 mm^2 precision [15, 20]. However, the average VN CSA of a healthy participant is c.2 $mm^{2,}$ and the reduction in PD is estimated at 0.4 mm^2, meaning that an accuracy of 0.1 mm^2 would seem to be a minimum threshhold when applying this method [78].

Moreover, as shown by the forest plot in Figure 3, a risk of publication bias must be taken into consideration. Avoiding observer bias with proper blinding is hard to achieve due to the prominent parkinsonian phenotype and direct patient-to-examiner contact during the ultrasound examination. Different attempts to overcome this problem have been tried. For instance, in one study an examiner blinded to the clinical diagnosis was unable to see the patients walking into the assessment room [14]. Another method involved calculating the cross-sectional area offline in image analysis software operated by a blinded evaluator [26]. Both approaches are far from ideal, as it seems unrealistic to entirely blind the primary sonographer.

Conclusions

Ultrasound examination is capable of recognising vagus nerve atrophy that is present in PD. Due to only a modest decrease in size, the utility of this method alone is rather limited for clinical diagnosis of the disease, but may provide important data about its pathogenesis. Such changes should be better studied implementing different disease phenotypes, vagus neurophysiological performance, and in correlation with other imaging and diagnostic methods. Clinical applications for PD recognition and non-motor symptom evaluation need to be determined in future research.

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