Transcutaneous Auricular Vagus Stimulation Improves Gait and Reaction Time in Parkinson's Disease

Recent studies have found that transcutaneous cervical vagus nerve stimulation (VNS) can improve gait symptoms in Parkinson's disease (PD).[1-3] Noninvasive VNS can be performed also on the auricular branch of the vagus nerve, with significant opportunities in terms of feasibility and costs. Data on the effects of transcutaneous auricular VNS (taVNS) in PD, however, are still missing. Hence we aimed at investigating the effects of taVNS on the gait of 12 patients with idiopathic PD, which were consecutively enrolled in a pilot-controlled study with a double-blind randomized crossover design, at the tertiary movement disorders clinic of our institution. Patients were selected according to the following criteria: (1) chronic levodopa therapy without a history of levodopa-induced dyskinesias, (2) walking difficulties but still able to walk unassisted (Unified Parkinson's Disease Rating Scale [UPDRS] Part II item 15 = 1 or 2), and (3) modified Hoehn & Yahr score <3 while *on* medication. Patients with early signs of cognitive impairment or atypical parkinsonism and individuals on anticholinergics and/or affected by any other known condition able to influence the gait were not included. Therapy changes between visits were not allowed. taVNS was delivered either on the left internal tragus (real) or the earlobe (control) in trains lasting 30 seconds each, composed of 600 pulses (frequency 20 Hz; duration 0.3 millisecond) repeated every 4.5 minutes for 30 minutes (six cycles) (Supporting Information Materials). Patients were randomized to one stimulation and after 1 week, all subjects were crossed over to the other. Patients were evaluated before and after the stimulation with UPDRS Part III, a flanker test (reaction time), a digital 10-m timed up and go (10mTUG) test performed in duplicate (Mon4t clinic, https://mon4t.com), and a Visual Analogue Scale (VAS 0–10, "How do you perceive your walking performance?"). The flanker is an acknowledged VNS-responsive parameter,[4] while the 10mTUG provides data on total time (stand, rotation, sit, and gait time), gait speed, stride length, number of steps, mediolateral sway, and swing amplitude.[5] The experiments took place in the morning while all of the patients were *on* levodopa. The patients' awareness about the condition (i.e., whether real or control) was verified with a questionnaire (Supporting Information Materials). Variables are presented as mean ± standard deviation. Data were tested for normality (Shapiro–Wilks test), compared through *t* test or Wilcoxon signed rank test for paired data (JMP software v16.0; SAS Institute Inc.), and corrected for multiple comparisons with the Benjamini–Hochberg method (false discovery rate set at 0.05).[3] Demographic and disease features are reported in Table S1. All 12 subjects completed both the real and the control stimulation; no dropouts were reported. Baseline data were similar between the two visits (Table S2). The UPDRS Part III and the Visual Analogue Scale scores showed an improvement both after the real and the control stimulation, likely because of a placebo effect; however, both scales showed a better trend following the real stimulation. Stride length, swing amplitude, gait speed, and gait time showed significant changes only after the taVNS. Rotation time, stand time, and sit time did not show any significant variation. Finally, the flanker reaction time improved after taVNS, corroborating our findings. Differences across variables and conditions are reported in Table 1. This is the first experiment reporting a systematic evaluation of taVNS in PD. In this sample of patients with mild-to-moderate PD, the taVNS in add-on to levodopa improved several objective gait parameters. Despite direct data on duration not being collected, the putative taVNS effect persisted for the time duration of the UPDRS motor assessment, the flanker test (mean completion time 52 ± 13.7 seconds), and two consecutive gait assessments (single 10mTUG test mean completion time 28 ± 7.3 seconds). The latter might give useful information for future biomarker (eg, neurophysiological) studies.[6] Preclinical studies showed that VNS can improve structural and functional aspects of PD.[7] Even though its mechanism of action is still debated, VNS can entrain the ascending cholinergic and noradrenergic pathways,[6,8] which are involved in cognitive processing and in locomotor abilities.[4,7] In this study, taVNS improved some dopamine-dependent gait parameters (eg, stride length).[9] If proven true, this would add information to the growing literature on the association between the vagus nerve and the dopaminergic system.[10] However, despite our results being in line with recent noninvasive cervical VNS experiments,[1-3] it is still not possible to draw a firm conclusion. Indeed, we collected data on the gait of patients with PD through a single sensor. This is a trusted methodology, but the use of a more comprehensive gait analysis system would allow a more precise analysis of gait and of gait-related PD issues (ie, freezing).[1,3] Moreover, the study should be replicated on a larger sample, allowing a more robust statistical methodology, eventually exploring VNS dosage and duration.[11] Nonetheless, given the manageability of the portable commercialized taVNS devices, they may be considered a valuable tool in the neuromodulation landscape of PD.

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TABLE 1 *Clinical and Digital Biomarker Differences Across Conditions*

	Control Stimulation			Real taVNS		
	T0	T1	*P* Value	T0	T1	*P* Value
UPDRS Part III	21.5 ± 7.8	19.7 ± 7.9	0.003*	22.5 ± 7.5	20.1 ± 7.2	0.002*
VAS	6.5 ± 1.6	7.6 ± 1.95	0.039	6.3 ± 1.5	7.6 ± 1.7	0.011*
Reaction time (s)	1.61 ± 0.68	1.53 ± 0.66	0.230	1.69 ± 0.52	1.50 ± 0.47	0.005*
Stand time (s)	1.83 ± 0.13	1.84 ± 0.16	0.846	1.80 ± 0.15	1.88 ± 0.15	0.129
Sit time (s)	4.29 ± 1.16	3.94 ± 0.92	0.080	3.95 ± 0.89	4.16 ± 1.19	0.392
Rotation time (s)	1.99 ± 0.07	1.99 ± 0.08	0.873	1.99 ± 0.08	2 ± 0.07	0.269
Total gait time (s)	19.57 ± 5.84	19.82 ± 7.19	0.569	21.95 ± 7.25	19.44 ± 5.8	0.001*
Gait speed (m/s)	1.25 ± 0.29	1.27 ± 0.35	0.531	1.14 ± 0.33	1.26 ± 0.31	0.029*
Steps (n)	25.7 ± 8.4	23.8 ± 8.1	0.056	25.3 ± 7.3	23.1 ± 8.1	0.264
Stride length (m)	0.61 ± 0.11	0.60 ± 0.13	0.722	0.58 ± 0.10	0.61 ± 0.11	0.005*
Sway (m)	0.06 ± 0.08	0.07 ± 0.10	0.726	0.04 ± 0.01	0.04 ± 0.008	0.078
Swing amplitude (m)	0.54 ± 0.13	0.55 ± 0.16	0.691	0.54 ± 0.17	0.59 ± 0.21	0.018*

taVNS, transcutaneous auricular vagus nerve stimulation; T0, baseline; T1, poststimulation; UPDRS, Unified Parkinson's Disease Rating Scale; VAS, Visual Analogue Scale.
*Statistically significant changes after correcting for multiple comparisons according to the Benjamini–Hochberg procedure.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.