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Non-invasive vagus nerve stimulation to target gait impairment in Parkinson's disease

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Gait impairments in Parkinson's disease (PD) are often present at diagnosis and respond selectively to treatment¹. Novel interventions targeting dopa-resistant gait impairments and their consequences - falls risk - are urgently needed. Recent evidence suggests neuronal cholinergic loss from the basal forebrain (nucleus basalis of Meynert) and brainstem (pedunculopontine nucleus) contribute to a functional decline in gait². A non-invasive technique that activates the cholinergic circuitry, which has gained recent traction in neurological disorders, is non-invasive vagus nerve stimulation (nVNS)³. The exact underlying mechanism of action of nVNS is poorly understood, but an indirect effect mediated through the cholinergic anti-inflammatory pathway has been postulated, through altered regulation of acetylcholine³. Therefore, our aim was to assess the effect of a single dose of nVNS on dopa-resistant gait characteristics (step time variability and step length variability)⁴ in a pilot feasibility study in PD.

Thirty participants with idiopathic PD (15 active and 15 sham) were recruited to the study. Participants were included if they were able to walk independently for two-minutes, had stable medication over the previous month and provided written consent. Those with significant cognitive impairment (MoCA ≤ 21), treated with anticholinergics and with contraindications to nVNS were excluded. **Figure 1A** displays the study design. Gait was measured within one hour both pre- and post- intervention during a two-minute continuous walk at a comfortable walking pace around a 25m circuit inclusive of a 7 x 0.6m instrumented walkway whilst ON dopaminergic medication. Participants in the active group received a single dose (120 seconds) of nVNS between the pre- and post-assessments with the gammaCore® handheld device which was applied to the left side of the neck. For the sham group, an identical device delivered an electrical stimulus that did not activate the vagus nerve. Absolute and percentage change pre- and post-intervention were compared by treatment groups using Mann-Whitney tests. A significant *p* value was classified as $\leq .05$.

Thirty-one participants were consented and 29 completed the study. There were no significant differences for baseline demographic (Age, gender, MDS-UPDRS part III, Hoehn and Yahr,

years of education and levodopa daily dose) or gait data between groups (**Supplementary Table 1**). In the active group, step time and step length variability decreased whereas an increase was identified in the sham group with step length variability reaching significance (-5.6 vs. 25.4% change for active vs. control group, $p=0.045$) (**Figure 1B**).

This exploratory study provides preliminary data suggesting dopa-resistant gait characteristics may improve with nVNS. The underlying mechanism of these findings may be related to amyloid pathology in PD, with cholinergic loss promoting amyloid- β deposition⁵ and amyloid- β precipitating cholinergic neuronal loss⁶. However, our study is limited due to the small and heterogeneous cohort. Larger trials should consider using multiple treatment doses of nVNS and a higher intensity of stimulation as moderate stimulation has demonstrated a significant effect on memory consolidation in Alzheimer's disease⁷. This small sham-controlled pilot study provides novel evidence of a potential beneficial effect of nVNS on gait in PD. Confirmation is required in a larger multi-dose trial.

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Author Roles:

RM: organisation and execution of research project, design and execution of statistical analysis, writing first draft of manuscript

AY: Design and execution of statistical analysis, writing first draft of manuscript

HH: Execution of research project, review and critique of manuscript

JPT: Conception and organisation of research project, review and critique of statistical analysis and manuscript

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