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Short communication

Caloric vestibular stimulation for the management of motor and non-motor symptoms in Parkinson's disease

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ABSTRACT

Introduction: A recent case study showed that repeated sessions of caloric vestibular stimulation (CVS) relieved motor and non-motor symptoms associated with Parkinson's disease (PD). Here we sought to confirm these results in a prospective, double-blind, randomized, placebo treatment-controlled study.

Methods: 33 PD subjects receiving stable anti-Parkinsonian therapy completed an active (n = 16) or placebo (n = 17) treatment period. Subjects self-administered CVS at home twice-daily via a portable, pre-programmed, solid-state ThermoNeuroModulation (TNM™) device, which delivered continually-varying thermal waveforms through aluminum ear-probes mounted on a wearable headset. Subjects were followed over a 4-week baseline period, 8 weeks of treatment and then at 5- and 24-weeks post-treatment. At each study visit, standardized clinical assessments were conducted during ON-medication states to evaluate changes in motor and non-motor symptoms, activities of daily living, and quality of life ratings.

Results: Change scores between baseline and the end of treatment showed that active-arm subjects demonstrated clinically-relevant reductions in motor and non-motor symptoms that were significantly greater than placebo-arm subjects. Active treatment was also associated with improved scores on activities of daily living assessments. Therapeutic gains were still evident 5 weeks after the end of active treatment but had started to recede at 24 weeks follow-up. No serious adverse events were associated with device use, and there was high participant satisfaction and tolerability of treatment.

Conclusion: The results provide evidence that repeated CVS can provide safe and enduring adjuvant relief for motor and non-motor symptoms associated with PD.

1. Introduction

In a single-case study, daily sessions of caloric vestibular stimulation (CVS) were associated with a ~50% reduction in both motor and non-motor symptoms of Parkinson's disease (PD) which were still evident 5 months after treatment cessation [1]. CVS was self-administered at home via a portable, solid-state, device that discharged time-varying thermal waveforms via ear pieces housed in a headset [2]. This result builds on evidence from laboratory experiments showing that vestibular stimulation in PD can increase functional neural connectivity and improve certain aspects of motor control [3–9]. Together, these data

prompted the current double-blinded, placebo-controlled study which sought to determine whether CVS might provide lasting, clinically-relevant improvement of both motor and non-motor features of PD.

2. Methods

PD patients were referred from clinical neuroscience services in West and East Kent (U.K.) or were recruited through local branches of the charity *Parkinson's UK*. Individuals were eligible for study inclusion if they met the diagnostic UK Parkinson's Disease Society Brain Bank Criteria for PD and experienced limitations to their activities of daily

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Table 1
Study demographics and baseline measures.

	Active	Placebo	p-value
n	16	17	
Demographics (mean(SD))			
Age (y)	68.0 (12.0)	71.3 (7.0)	0.337
Male sex, No. (%)	10 (62.5%)	14 (82.4%)	0.201
Years of education +	15 (12, 21)	14 (12, 22)	0.863
Years since PD diagnosis +	10 (2, 28)	5 (2,14)	0.009
Years on dopamine replacement therapy +	10 (1, 28)	5 (2, 14)	0.025
VAS score +	7 (1, 10)	7 (1, 10)	0.630
Levodopa equivalent daily dose	843.6 (409.0)	621.6 (491.5)	0.170
Concomitant therapy at baseline, n (%)			
Oral levodopa-based therapy	15 (93.8%)	17 (100%)	0.295
Dopamine agonist	11 (68.8%)	7 (41.1%)	0.166
MAO-B inhibitor	3 (18.8%)	5 (29.4%)	0.688
COMT inhibitor	6 (37.5%)	3 (17.6%)	0.438
Amantadine	2 (12.5%)	2 (11.8%)	1.000
Anticholinergic	1 (6.3%)	1 (5.8%)	1.000
Antidepressant/ Anti-anxiety	6 (37.5%)	6 (35.3%)	1.000
Duodopa	1 (6.3%)	0 (0.0%)	1.000
Incontinence	4 (25.0%)	3 (5.9%)	1.000
Sleep Aid	1 (6.3%)	2 (11.8%)	1.000
Pain/cramping	3 (18.8%)	5 (29.4%)	0.688
Laxative	0 (0.0%)	1 (5.9%)	1.000
Central acteylcholinesterase inhibitor	1 (6.3%)	2 (11.8%)	1.000
Blood Pressure	6 (37.5%)	4 (23.5%)	0.465
Deep Brain Stimulation	0 (0.0%)	0 (0.0%)	1.000
Baseline assessment scores (average ± SD)			
MDS-UPDRS			
Part I	17.3 (5.8)	15.8 (4.9)	0.441
Part II	23.0 (9.3)	21.7 (6.1)	0.644
Part III	48.8 (16.7)	42.3 (16.0)	0.262
Hoehn Yahr +	3.0 (2.0, 4.0)	2.0 (2.0, 4.0)	0.128
PIGD	8.5 (4.3)	7.1 (4.5)	0.344
NMSS total score			
Domain 1: Cardiovascular/falls +	129.0 (31.7)	125.0 (31.5)	0.714
	0 (0.0, 12.0)	0.5 (0.0, 10.5)	0.666
Domain 2: Sleep/fatigue	21.8 (6.2)	19.9 (9.3)	0.476
Domain 3: Mood/cognition	23.8 (12.5)	25.7 (16.6)	0.714
Domain 4: Perceptual /hallucinations +	0 (0, 16)	0 (0, 15)	0.425
Domain 5: Attention/memory	14.8 (11.6)	15.4 (9.1)	0.869
Domain 6: Gastrointestinal tract	13.1 (8.5)	11.9 (6.6)	0.658
Domain 7: Urinary	20.7 (8.4)	17.3 (9.0)	0.273
Domain 8: Sexual function +	21.0 (1.0, 24.0)	18.0 (1.0, 24.0)	0.357
Domain 9: Miscellaneous	12.1 (6.3)	13.4 (5.9)	0.520
MoCA +	25.0 (20.5, 28.5)	26.0 (10.0, 29.0)	0.689
HADS Anxiety +	4.0 (1.0, 14.5)	5.5 (1.0, 13.0)	0.459
HADS Depression +	6.75 (2.0, 14.5)	6.5 (2.5, 16.5)	0.742
Epworth Sleepiness Scale	14.7 (5.4)	10.4 (6.2)	0.044
Fatigue Severity Scale	47.8 (6.8)	39.9 (10.4)	0.016
TUG +	14.1 (7.6, 27.1)	11.4 (6.5, 213.0)	0.817
10 meter walk self-paced +	9.4 (5.3, 29.8)	6.6 (4.3, 38.7)	0.168
10 meter walk fast-paced	5.3 (1.1)	4.7 (1.3)	0.154
2 minute walk	71.0 (24.9)	80.6 (32.3)	0.349
PDQ-39	33.7 (10.4)	30.3 (8.8)	0.318
Modified Schwab & England	69.5 (32.5, 82.5)	70.0 (40.0, 95.0)	0.338
EQ-5D-5L	0.63 (0.14)	0.66 (0.08)	0.451
SF-12 PCS	32.0 (5.9)	35.9 (5.7)	0.061
SF-12 MCS	48.53 (10.6)	46.5 (8.6)	0.557

Note: + indicates non-normal distribution of data. In these cases, values are reported as median ± range low value, high value. Differences between groups were evaluated using Student's t test (in the case of normal distributions), Mann-Whitney U tests (in the case of non-normal distributions) or Fisher's exact test to compare proportions. VAS provided a patient-reported measure for perceived efficacy of levodopa-based therapies for addressing PD symptoms.

living. Patients were receiving stable regimens of anti-Parkinsonian medications. Patients with prior exposure to neurostimulation and/or known inner ear pathology were excluded from the study.

2.1. Study design

Eligible subjects completed a 4-week baseline evaluation comprising assessments repeated in the first and fourth week. They were randomized (1:1 ratio) to active or placebo treatment groups. CVS treatments were self-administered at home for 8 weeks. Behavioral assessments were repeated midway through the 8-week treatment period, at the end of treatment, and then 5 weeks later. Subjects who remained contactable and consented to remain blinded to treatment allocation were also evaluated at approximately 6 months after treatment. All evaluations were conducted at the homes of subjects by the same blinded clinical researcher. Assessments were performed when subjects were in the ON medication state (timed to occur at the same time relative to the last dose of anti-Parkinsonian medication). The outcome measures can be found in Table 1.

Approval was obtained from the East Midlands NHS research ethics committee. Written informed consent was obtained from all subjects at study enrollment. The study was pre-registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov) as NCT02703844.

2.2. Stimulation protocol

CVS was administered using the TNM™ Device (Supplemental Fig. 1) recently cleared for market entry in both the United States (by the FDA via DEN170023) and the European Union (by BSI via EC Certificate CE 651494) for the prophylactic treatment of episodic migraine in adolescents and adults 12 years and older (U.S.) and adults (E.U.) [10]. The TNM™ Device is an Investigational Device that is limited by United States and European Law to Investigational Use. It can only be used by PD patients in the setting of a clinical trial and is not available for sale. CVS treatment involved lying on a 22°-elevated wedge pillow to orient the horizontal semi-circular canal vertically (thereby maximizing vestibular activation). Active treatment involved the simultaneous delivery of a time-varying, warm, saw-tooth thermal (37 °C–42 °C) stimulus to one ear and a cold saw-tooth thermal (37 °C–17 °C) stimulus to the other ear for approximately 19-min (Supplemental Fig. 2). Subjects were instructed to separate their twice-daily treatments by at least 1 h. Every 2 days the warm and cold waveforms were switched from one ear to the other to avoid the possible induction of a lasting, lateral, vestibular asymmetry [11]. By slow warming and cooling of inner ear structures, it was possible to avoid vertigo and nausea that can result from chilled water irrigation. In the placebo treatment condition, subjects underwent the same 19-min treatment choreography twice daily; however, no power was delivered to the heating and cooling elements. To maintain treatment blinding, treatment was discussed as brainstem modulation and no reference to the thermal stimulus was made. Subjects were told that they might or might not feel temperature changes in their ears and that this would not be an indicator of active or placebo treatment; rather, temperature changes are naturally felt by some people and not by others. Subjects were told that they had a 50% likelihood of receiving either placebo or active treatment. Those allocated to the placebo treatment arm were promised the later opportunity to receive active treatment if the study showed positive outcomes.

2.3. Statistical analyses

Efficacy analysis was conducted on the per protocol (PP) dataset at the end of active treatment and at 5-week and 24-week follow-ups. It included only those subjects who completed the study without a major protocol violation. Subjects who withdrew or changed dose or type of medications used to treat symptoms associated with PD prior to the end

Table 2
Per protocol statistical results

Outcome Measure	Change from baseline at week 12				Change from baseline at week 17				Change from baseline at week 36			
	Active Mean	Placebo Mean	Therapeutic Gains	95% CI	Active Mean	Placebo Mean	Therapeutic Gains	95% CI	Active Mean	Placebo Mean	Therapeutic Gains	95% CI
	16	17			14	17			12	15		
Sample size	16	17										
Movement Disorder Society Sponsored Unified Parkinson's Disease Rating Scale	-5.6	-2.3	-3.4*\$	-6.2 to -0.5	-6.3	-0.1	-6.2*\$	-8.9 to -3.4	-1.5	-1.9	0.3	-4.4 to 5.0
Part I: Non-Motor Aspects of Experiences of Daily Living	-5.3	-0.7	-4.6*\$	-6.7 to -2.5	-4.7	-0.4	-4.3*\$	-7.4 to -1.2	-1.7	0.5	-2.2	-5.3 to 0.9
Part II: Motor Aspects of Experiences of Daily Living	-10.8	-3.9	-6.9*\$	-13.4 to -0.5	-11.8	2.9	-14.7*\$	-21.6 to -7.9	-5.0	0.8	-5.7 \$	-14.3 to 2.9
Part III: Motor exam	-1.4	-0.9	-0.6	-2.4 to 1.2	-1.3	-0.6	-0.6	-2.7 to 1.4	0.4	0.6	-0.2	-1.7 to 1.4
Postural Instability/gait difficulty + Non-Motor Symptom Scale	-39.7	-6.5	-33.2*	-51.4 to -15.1	-41.0	-0.4	-40.6*	-57.6 to -23.6	-22.4	-11.5	-10.9	-35.9 to 14.1
Domain 1: Cardiovascular including falls +	0.0	0.0	0.5	-0.5 to 3.5	0.0	-0.5	0.0	-1.5 to 1.5	-0.4	-0.6	-0.2	-1.7 to 1.4
Domain 2: Sleep/fatigue	-5.8	-4.4	-1.4	-6.0 to 3.2	-7.7	-2.5	-5.1*	-8.3 to -2.0	-3.7	-3.7	-0.1	-4.7 to 4.6
Domain 3: Mood/cognition	-10.8	3.4	-14.2*	-21.8 to -6.5	-10.5	3.8	-14.3*	-22.3 to -6.4	-6.6	-1.2	-5.4	-20.1 to 9.3
Domain 4: Perceptual problems/hallucinations +	0.0	0.0	0.0	-1.0 to 0.5	0.0	0.0	0.0	-1.0 to 0.5	0.0	0.0	0.0	-1.5 to 1.0
Domain 5: Attention/memory	-6.0	-0.3	-5.7*	-10.3 to -1.1	-5.9	2.2	-8.1*	-13.0 to -3.1	-2.5	-2.1	-0.4	-5.6 to 4.8
Domain 6: Gastrointestinal tract	-5.2	-2.3	-2.9	-7.2 to 1.5	-5.4	-1.5	-3.8*	-7.5 to -0.2	-3.0	-1.9	-1.1	-5.7 to 3.4
Domain 7: Urinary	-6.6	-1.3	-5.3*	-10.4 to -0.2	-5.7	-2.9	-2.9	-8.5 to 2.7	-3.9	-2.3	-1.6	-6.4 to 3.1
Domain 8: Sexual function +	-1.8	0.0	-3.0*	-5.0 to -1.0	0.0	0.0	-3.0*	-6.0 to 0.0	0.0	0.5	-1.0	-4.0 to 1.5
Domain 9: Miscellaneous	-3.1	-0.6	-2.5	-5.5 to 0.6	-2.7	1.0	-3.7*	-7.0 to -0.4	-0.2	0.1	-0.4	-3.6 to 2.8
Montreal Cognitive Assessment	2.5	0.3	2.2*	1.0 to 3.5	2.6	-0.4	3.0*	1.5 to 4.5	1.5	-0.5	2.0	0.0 to 4.0
Hospital Anxiety and Depression Scale	-1.7	-0.7	-1.1	-2.8 to 0.7	-2.9	-0.4	-2.5*	-4.4 to -0.7	-1.6	0.6	-2.2	-4.6 to 0.2
Anxiety Score	-1.5	-0.3	-1.2	-2.7 to 0.2	-1.2	0.7	-1.9	-4.0 to 0.2	-1.3	0.0	-1.4	-3.9 to 1.2
Depression Score	-2.2	0.3	-2.5	-5.4 to 0.4	-1.7	-0.7	-1.0	-3.8 to 1.8	-3.3	0.9	-4.1*	-7.0 to -1.3
Epworth Sleepiness Scale	-3.5	-1.4	-2.8	-8.4 to 3.5	-4.9	0.0	-4.9	-10.5 to 0.7	-1.4	-1.4	0.0	-6.3 to 6.3
Fatigue Severity Scale												
Total Score												
Timed-up-and-go												
Time to complete + 10 meter walk	-2.0	0.0	-3.1*	-7.5 to -0.0	-2.7	0.5	-2.4	-4.6 to 2.1	2.6	-1.1	3.9	-1.0 to 33.8
Self-paced walk time (seconds) +	-0.8	-0.1	-0.9*	-2.0 to -0.2	-1.0	0.4	-1.3*	-2.5 to -0.4	-0.1	-0.4	-0.1	-1.6 to 1.4
Fast-paced walk time (seconds)	0.2	0.2	0.0	-0.6 to 0.5	0.1	0.4	-0.3	-0.9 to 0.3	0.2	0.2	0.0	-1.1 to 0.9
2 minute walk												
Distance (meters)	1.2	-0.7	1.9	-12.2 to 16.0	6.5	-3.7	10.2	4.0 to 24.4	-8.0	2.6	-10.6	-26.8 to 5.6
Parkinson's Disease Questionnaire - 39												
Summary Index Score	-8.1	-5.2	-2.9	-7.8 to 2.0	-7.0	-2.8	-4.2	-9.2 to 2.5	-3.3	0.6	-3.9	-10.4 to 2.6
Modified Schwab and England Activities of Daily Living Scale												
Total Score	10.7	0.4	10.2*	1.4 to 19.0	7.7	-1.9	9.5*	1.0 to 18.1	-2.2	-1.2	-1.0	-12.7 to 10.8

(continued on next page)

Table 2 (continued)

Outcome Measure	Change from baseline at week 12				Change from baseline at week 17				Change from baseline at week 36			
	Active Mean	Placebo Mean	Therapeutic Gains	95% CI	Active Mean	Placebo Mean	Therapeutic Gains	95% CI	Active Mean	Placebo Mean	Therapeutic Gains	95% CI
Index Score	0.07	0.04	0.03	-0.05 to 0.11	0.00	-0.03	0.02	-0.08 to 0.13	-0.08	0.00	-0.08	-0.25 to 0.10
SF-12 Health Survey Physical Composite Score	5.3	1.8	3.5	-1.1 to 8.1	2.7	1.4	1.3	-4.0 to 6.5	0.4	2.5	-2.1	-7.5 to 3.3
Mental Health Composite Score	3.3	-0.2	3.6	-1.4 to 8.6	2.8	-1.3	4.0	-1.8 to 9.9	-1.0	-1.6	0.6	-5.7 to 6.9

Therapeutic gains are calculated as Active - Placebo group change scores. + Medians and median difference (Hodges-Lehmann estimator of median difference based on differences of all possible pairs of individual values, one from each treatment arm) and non-parametric Hodges-Lehmann confidence intervals. *Statistically significant ($p < 0.05$), † meets or exceeds minimal clinically important difference (MCID). End of treatment assessment (week 12), 5 week post-treatment follow up assessment (week 17), 24 week post-treatment follow up assessment (week 36).

of the treatment period were excluded from the PP analysis. The intention-to-treat analysis is reported elsewhere [12].

Outcomes were investigated using analysis of covariance to compare the change in the mean response (from the average of week 1 and 4 baseline scores) across treatment groups using an alpha of 0.05. The outcomes were adjusted for baseline symptom severity by including the baseline measure as a covariate. Outcomes with non-normal distributions were analyzed using Wilcoxon Rank Sum tests to compare the median change in response across treatment groups. The Hodges-Lehmann method was used to calculate median difference and confidence intervals. Analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

2.4. Missing data

Less than 5% of data were missing at week 12 in the PP dataset for all outcomes, with the exception of the 10-m fast-paced walk (12% missing), 2-min walk (6% missing) and the Timed-Up-and-Go (6% missing).

3. Results

Forty-six subjects on stable anti-Parkinsonian medication were randomized and received at least one CVS treatment. Of these, 33 subjects completed the full treatment period with no major protocol violations and were included in the PP analysis. Thirty-one and 27 subjects, respectively, completed the 5-week and 6-month follow-up assessments. The attrition rate was similar for the active and placebo treatments. The demographics and assessment scores at baseline and concomitant medications were similar between the active and placebo groups (Table 1, Supplemental Table 1). The clinical assessment results for the PP group are summarized in Table 2 and illustrated in Supplemental Fig. 3. Individual outcome data can be found in the following online repository: <https://data.mendeley.com/datasets/m7ths6gdv9/1>.

3.1. Non-motor symptom (NMS) outcomes

Evaluation of the change in MDS-UPDRS Part I (Non-Motor Aspects of Experiences of Daily Living) from baseline to the end of the treatment period revealed that the active group experienced a significantly greater reduction in the overall burden of NMS relative to the placebo treatment group. Therapeutic gains for this assessment were greatest 5 weeks after the cessation of treatment although change scores at both time-points surpassed a previously established minimal clinically important difference (MCID) [13]. Likewise, active CVS treatment subjects demonstrated significantly greater reductions in NMSS total score than the placebo arm subjects at the end of treatment and which again showed the largest therapeutic gains at the 5-week follow-up assessment. Substantive improvements were demonstrated in most NMSS sub-domains. At the individual subject level, 14 of the 16 active PP subjects demonstrated reductions ≥ 10 points on one or more domains of the NMSS (Supplemental Fig. 4). Supplemental exploratory *post-hoc* analysis indicated that there were no interactions with sex, age, time since PD diagnosis, time on anti-Parkinsonian medication, or the VAS score and the observed treatment responses for the NMSS total score. Active arm subjects also demonstrated statistically significant improvements in MoCA scores that persisted through the 5-week follow-up.

3.2. Motor symptoms, ADLs and complications

Active arm subjects demonstrated durable improvements in the MDS-UPDRS Part II (motor aspects of experiences of daily living) and Part III (motor exam) scores that were significantly greater than those for the placebo treatment group, with therapeutic gains exceeding the

MCIDs [13,14]. Therapeutic responses were not influenced by sex, age, time since diagnosis, time on anti-Parkinsonian medication, or VAS. Statistically significant differences were also observed in the Modified Schwab & England ADL scale, the 10-m self-paced walk and the Timed-Up-and-Go. Active treatment was also associated with reductions in the MDS-UPDRS Part IV (motor complications) driven primarily by reduced dyskinesias (Supplemental Table 2).

3.3. Quality of life

Active treatment subjects demonstrated improvements in PDQ-39 scores relative to baseline at weeks 12 and 17 that exceeded the MCID [15]. However, the therapeutic gains remained as non-significant trends.

3.4. Blinding

At the 5-week follow-up, subjects were asked to guess their treatment allocation. No active subjects guessed that they had received active treatment: 9 guessed placebo treatment and 6 said that they were unsure of their allocation (1 response was missing). 1 placebo treatment subject guessed receiving active treatment, 12 guessed placebo treatment and 4 were unsure.

3.5. Safety

Thirty four adverse events were reported in the 46 randomized subjects: 24 in the active group and 10 in the placebo group. The likely cause of all adverse events was determined by independent clinical adjudication. Three adverse events were classified as “serious”, but none was deemed to be related to device use. Four adverse events (i.e., ear discomfort, dizziness/motion sickness and migraine) were considered to be “possibly” related to device use; however, none was considered to be severe, and all resolved after the cessation of device use. All other adverse events were minor and were most likely attributable to PD rather than to study involvement. For full details, see Ref. [12].

3.6. Device usability and satisfaction

All 33 PP subjects completed a device-usability survey at the end of the treatment period. Twenty-five subjects found the device ‘easy to use at home’, 2 had no opinion and 6 subjects said that the device was not easy to use but continued anyway. Nearly all subjects found the actual time spent treating as ‘enjoyable’ or ‘acceptable’, with 1 expressing no preference and 2 describing it as ‘challenging to maintain’. When asked to rate their overall experience with the device, 5 active and 5 placebo treatment subjects described it as ‘very positive’, 7 active and 11 placebo treatment subjects described it as ‘somewhat positive’, 2 active subjects described it as ‘somewhat negative’ and 2 active and 1 placebo treatment expressed no preference.

4. Discussion

The results from this randomized, double-blind, placebo-controlled study in PD patients demonstrate that twice daily active treatment for 8 weeks with the CVS device was associated with clinically-relevant improvements in both motor and non-motor features of PD. These improvements were detected at the end of active treatment and, in the majority of instances, therapeutic gains were greater 5 weeks after treatment cessation. At 6 months follow-up, most of the gains had returned to baseline status although there was some evidence of residual effect. These clinical improvements were obtained without significant safety concerns; no serious adverse events likely to be device-related were reported, and subjects described their experience with the device as largely positive.

Given the robust clinical effects, the failure of active-treatment subjects to accurately guess their treatment allocation was surprising. This lack of awareness may partly be explained by a difficulty perceiving the gradual symptom reduction which occurred over days to weeks in comparison with the visible motor improvements that occur more abruptly with anti-Parkinsonian medications. Additionally, some patients with PD do not strongly associate their NMS with Parkinsonism [16] which, in the current study, may have made some subjects less likely to attribute their NMS improvement to device treatment.

The successful concealment of allocation in this study provides good reason to suggest that the clinical improvements were driven by more than just a placebo response. Rather, the highly similar trajectory of response curves in the active group from week 0 to week 36 across several independent measures of both motor and non-motor function support the likelihood that efficacy is driven by a genuine physiological mechanism of action which, given the durability of effect, may involve long-term plastic change [17,18]. CVS is known to activate a variety of ascending cortical and subcortical pathways implicated in PD symptomatology [19,20]. Its means of induction sets it apart from all known pharmacological and other neuro-modulatory procedures which are non-endogenous in nature and chemically/anatomically localized. Coupled with the diffuse clinical effects reported here, these characteristics speak to domain-general mechanisms of action such as those associated with cortical entrainment and neurovascular coupling which help to synchronize neural activity. In line with this, we recently showed that the CVS waveform applied in this study induced oscillations in cerebrovascular dynamics suggestive of pontine entrainment [2]. Future studies will seek to further elucidate these mechanisms in parallel with larger-scale clinical evaluation.

Author's roles

D.W. was involved in all study phases; A.M. assisted with study design, helped coordinate and execute the study and contributed to manuscript preparation, T.P. and M.Slade. conducted all statistical analyses, statistical interpretation, statistical reporting and provided manuscript critique; M.B. assisted with the study design, referred subjects, provided clinical oversight during study, assisted with data interpretation and provided manuscript critique; M.Sakel assisted with study design, provided clinical oversight during study, assisted with data analysis and interpretation, and provided manuscript critique; S.B. assisted with statistical analyses, manuscript writing and review; L.S. provided manuscript critique, P.L. assisted with data interpretation and helped write the manuscript, K.A. helped coordinate the study, assisted with statistical analysis and interpretation and helped write and review the manuscript.

Financial disclosure

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Declaration of interest

K.A. reports receiving compensation and ownership interests in Scion NeuroStim, LLC (SNS), S.B. reports receiving compensation from SNS and L.S. reports ownership interests in SNS.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2019.05.031>.

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