Caloric Vestibular Stimulation to Treat Symptoms Associated with Parkinson's Disease.

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Scientific Protocol Version #9a

1. Abstract
Applicant Details

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Parkinson's Disease (PD) is a nationwide public health problem, inflicting a complex constellation of physical and neuropsychiatric symptoms which are shown to progress with time. This research will investigate the potential of caloric vestibular stimulation (CVS), a non-invasive form of brain stimulation, as a treatment for individuals who suffer from Parkinson's Disease. CVS works by cooling or warming the external ear canal which in turn activates the vestibular (aka balance) organs, fooling the brain into reacting as if a real head movement has occurred. Corresponding metabolic changes linked to plastic change and recovery are subsequently elicited across many brain areas. CVS can be administered without any technical expertise or supervision, so is suitable for home-based use.

We plan to recruit a diverse sample of 32 patients with idiopathic Parkinson's disease from outpatient NHS settings across South East England. We will investigate whether core cognitive and physiological deficits are responsive to stimulation by comparing participants' performance on behavioural and physiological measures after baseline and either active or placebo stimulation phases with the aim of drawing initial insights into the application of CVS within this population. The study design is based on a single-case study that recently demonstrated durable, clinically meaningful gains in the motor and cognitive symptoms of PD.

Project Duration

12 months

2. Background

2.1 Health need

Parkinson's Disease (PD) can be defined as a progressive degenerative neurological disorder (Hoehn & Yahr, 1967; Leentjens, et al. 2002). PD is mainly known and recognized as a disorder affecting motor functioning. Recent literature however emphasizes the effects that PD has on cognitive functioning such as deteriorating memory with dementia eventually affecting the majority of patients (Lehrner et al. 2014).
Parkinson's Disease currently affects over 120,000 people in the UK alone (National Statistics Office, 2009). It is known to be the second most common neurodegenerative condition in the population beyond the age of 60, affecting males more often than females (von Campenhausen et al. 2005). In the US, the number of people diagnosed with PD is approximately 630,000 and according to Stacey Kowal, the estimated cost of care (medical and non-medical) for patients with PD is $14.4 billion or $22.800 per person (Kowal, 2013). Despite this high prevalence and expenditure, PD remains uncurable and the

most common form of therapy becomes ineffective after years of application (Tolosa et al. 1998). The difficulty of finding a cure for PD is largely due to the fact that the cause for degeneration of dopaminergic cells is still unknown (Hesse et al. 2003).

PD results in damage to the dopaminergic cells in the brain, leading to a complex constellation of physical (resting tremor, bradykinesia, posture instability, sleep disturbance) and neuropsychiatric symptoms encompassing mood disorders (anxiety and depression) and cognitive dysfunction (e.g. memory, attention, executive function) (Alzahrani et al. 2015). Finding a treatment which can respond to the heterogeneous facets of PD is greatly needed given the consequences of physical disability and premature requirement of care for the patients suffering from PD, the resulting burden for families and the societal costs (Porter et al. 2010).

Current treatments for PD are centered around pharmacotherapy. Levodopa is commonly regarded as the "gold standard" treatment (LeWitt, 2015), although current literature demonstrates that the progressive symptoms of PD become increasingly refractory to drug treatments over time (Clarke, Worth, Grosset, & Stewart, 2009), resulting in side effects (e.g. bradykinesia) and shorter periods of effectiveness for each oral dose as well as unpredictable fluctuations ("on-off" periods) and dyskinesia (Olanow, & Obeso, 2000). To reduce the effects of oral intake of levodopa, infusion therapies have been given much consideration. They provide more constant dopaminergic stimulation which mimics the normal physiological state (Clarke et al., 2009), allowing not only smoother motor control but also reduced dyskinesia. Such treatments are however expensive and require considerable, if not constant, nursing support due to the complexity of administration via syringe driver or pump (Santos-Garcia et al., 2012).

Other treatments favoured, normally adopted only in advanced stages of PD, include deep brain stimulation (DBS) which involves implanting electrodes most commonly into subthalamic nuclei, which are then overstimulated. Such overstimulation of subthalamic nuclei results in a reduction of dyskinesia and the "off time" (Pahwa, et al., 2006). The literature also reports that patients undergoing DBS experience better control of motor symptoms as well as better quality of life (Moro, Lozano, & Pollak, 2010). DBS however might lead to unpredictable side effects, such as increased impulsivity and delirium (Klingehoefer et al., 2014). Furthermore, it is worth highlighting that DBS is a very expensive surgical procedure with potential complications. These may vary from manageable ones such as device dislocation (1.6%) and impaired wound healing (3.2%) to severe ones including life-threatening events, which affect up to 16% of cases (Bronstein, Tagliati & Alterman, 2011). There is also a risk of reduced verbal fluency and apathy as well as diminished performance during attention-demanding tasks following administration of DBS (Jahanshahi, 2013). Patients are also required to remain in hospital following the procedure and thus the cost-effectiveness of such therapy is debatable.

2.2 Proposed Solution

CVS may offer some benefit here. It is a well-established diagnostic method with an excellent history of safety. The use of CVS as therapy has been tried sporadically in the past, but no longitudinal RCT's have been undertaken. The classical CVS procedure works by irrigating the external ear canal with cold or warm water. This alters the density of fluid inside the semi-circular canals, resulting in thermo-convective flow, which in turn stimulates the vestibular afferent nerves and brain stem nuclei (Been et

al., 2007). The vestibular system is a complex network, which plays a crucial role in a variety of everyday functions such as our sense of wellbeing, spatial orientation, visual movement (balance/ posture) and autonomic regulation. The labyrinth, a small organ located within the inner ear, forms the peripheral receptor. This receptor connects with centres at all levels within the central nervous system (Tascioglu, 2005) forming a widely distributed vestibular cortical network. Neuroimaging studies utilizing CVS to activate the vestibular system have revealed widespread activation across cortical and subcortical structures including the anterior cingulate cortex, mid brain, temporoparietal cortex and the insular cortex (Suzuki et al., 2007). Thus, by modulating activity in the ascending vestibular pathways, the procedure can potentially relieve a variety of symptoms.

The ascending projections from the vestibular brainstem nuclei are receiving growing interest as a potential therapeutic pathway in Parkinson's Disease (PD). In a recent hemi-parkinsonian rat study, artificial stimulation of the vestibular nerves via transmastodial galvanic current was associated with improved locomotory ability and allied increases in GABA concentration in substantia nigra pars reticulate (Samoudi et al., 2012). In human PD studies, galvanic vestibular stimulation has been shown to spontaneously reduce postural sway (Pal et al., 2009), postural response time (Samoudi et al., 2015)], and also lead to a quickening of bradykinesic rest-to-active transitions in the wrist and trunk (Pan et al., 2008). In addition, recent investigations applying artificial vestibular stimulation have begun to reveal its therapeutic potential in remediating neurological conditions such as mania (Dodson, 2004); anosognosia (insight into illness) (Cappa et al., 1987; Levine et al., 2011); pain (Ramachandran et al., 2007); neglect (Adair et al., 2003, Wilkinson et al., 2014), hemianesthesia (Bottini et al., 2005) and aphasia (Wilkinson et al al., 2013).

The use of CVS for therapeutic purposes has been stymied by the crude irrigation-based devices used in diagnostics. The development of a solid-state CVS device (Scion NeuroStim, Raleigh, NC) has provided a therapeutic tool that enables controlled CVS administration in a home environment. CVS is a particularly innovative method of vestibular stimulation because it can be administered with little or no technical expertise; it simply requires an ear piece to be fitted within the external ear canal (like a headphone or ear plug) and a pre-set thermal waveform to then be delivered by a small, inexpensive control unit (see figure 1). Unlike other rehabilitation techniques, no dedicated space, technical staff or lengthy setup procedures are required. Rather, stimulation can be administered quickly and easily by a ward nurse or carer or the patient himself/herself while the patient is supine on a wedge pillow.

Figure 1. The stimulation apparatus comprised temperature controlled earpieces mounted within the headset, and the AC powered control unit.

Importantly, the solid-state CVS device creates time-varying thermal waveforms and a different waveform pattern can be delivered to each ear, leading to a wide variety of potential therapeutic combinations. The application of a constant temperature CVS stimulus, such as that from a conventional irrigator, results in adaptation of the vestibular organ within 2-3 minutes, thus terminating the modulatory effect. By varying the thermal profile in a controlled manner over time, adaptative effects are avoided and vestibular neuromodulation can be delivered over extended times. The controlled manner of delivery also enables consistent treatment from session to session.

2.3 Primary Objective

Although current literature demonstrates the potential therapeutic value of vestibular stimulation in PD, the results were acquired under highly prescribed, controlled laboratory conditions, utilized a narrow range of mostly experimental rather than clinical outcomes, and perhaps most importantly did not show if the effects persisted beyond a few hours. To be of rehabilitative relevance, it now needs to be demonstrated that vestibular stimulation can induce durable, clinically meaningful improvements in both the motor and non-motor symptoms of PD. The aim will be to evaluate whether repeated sessions of caloric vestibular stimulation can improve the persistent and disabling symptoms of PD.

2.4 Overview of the Design Study

To investigate the impact of CVS on PD, a diverse sample of 32 individuals diagnosed with Parkinson's disease from community and outpatient settings will be recruited and will have an equal chance of receiving active or placebo stimulation.

Participants will first complete an initial 4 week period of baseline assessment to quantify their deficits and isolate any improvements due to natural recovery. Next the participants will be divided; one group will proceed to a phase of active stimulation where they will undergo two twenty minute sessions of CVS each day. In order to control for placebo effects, the other group will receive sham stimulation where two 20 minute sessions of inactive stimulation will be given each day.

Participants will complete a battery of physiological and behavioural assessments at the end of every four weeks to monitor their progress on the core symptoms of interest. At the end of the study all participants will re-do the full baseline assessment to determine whether any of their symptoms have responded to the stimulation. Participants will undergo an EEG test at baseline and then at the end of the study protocol to assess changes at the neuro-physiological level. Additionally, all patients will be subject to a short video recording at baseline and at the end of the protocol to provide qualitative evidence to clinical audiences and potential funders post-study.

2.5 End-users and benefits

The end-users will be patients who suffer from PD and their carers. In the long term, outpatient and community staff responsible for delivering therapy may also benefit from reductions in workload due to the minimal set-up of the device which can be administered by patients themselves or their families. Additionally, researchers in the fields of neurorehabilitation, vestibular processing and cognitive disciplines may benefit from the insights produced by this study.

2.6 Safety

Vestibular stimulation is an inherently safe procedure that has been applied to many different populations over the last 100 years. It has been extensively used as a diagnostic test of vestibular impairment and to assess brainstem function within coma patients, where it is traditionally applied to the external auditory canal using cold-water irrigation or puffs of cool air. This procedure typically produces signs of nystagmus and reports of nausea and vertigo amongst subjects. However, following recent advances in biomedical science, the current study will use a computer-controlled device (manufactured by Scion Neurostim, LLC) that mirrors the effect of cold-water irrigation by means of a thermoelectric probe that sits inside the external ear canal and conducts temperature gradients to and from the vestibular organs. Importantly, the device mitigates side effects by controlling the time-rate-of-change of temperature and is well tolerated. The earpiece is specifically designed to prevent intrusion into the bony portion of the ear canal, and therefore there is no invasive contact or risk to the tympanic membrane.

As noted earlier, unlike traditional CVS methods, the Scion device is able to cycle the waveform between cool and warm temperatures avoiding adaptation and enabling longer-term stimulation sessions to be conducted (given the practicality and comfort of the device itself). The approach also permits experimenters to closely control the temperatures delivered; here we will only work within a perceptually mild range of temperatures, as previous studies indicate that extreme temperatures are not needed to achieve efficacy.

The device itself is a prototype that has been manufactured at a site in the US that has followed ISO 13485 controls. The FDA has supplied an opinion letter that classifies the device as "non-significant risk". Within the last few years, the device has been approved in several US universities for research use in other neurological populations, including those with intractable paediatric epilepsy and chronic migraine. Here in the UK, the device has been applied to migraine sufferers, healthy volunteers stroke patients and individuals in permanent vegetative state following traumatic brain injury. These research studies have utilised stimulation protocols comparable to those that we plan to use here and have reported positive outcomes with no serious side-effects attributable to study participation.

3. Preparation of the Intervention

The temperature-variable earpieces are integrated into a padded headset that is worn by the participant. It is activated by a microprocessor-based control system that executes the pre-planned thermal waveforms and includes safety lockouts if a fault condition occurs during use. Stimulation protocols (active vs. sham) will be pre-programmed onto the devices for participants.

The control unit has a small touch screen which is easy to use. To begin stimulation, patients will have to click a green arrow and a tone will be emitted to indicate that it has begun. The screen will also switch to a stimulation mode, where a blue horizontal line will turn red as the stimulation is completed. Once complete, a tone will be emitted again. In case of malfunction, a command will appear on the screen and stimulation will be immediately discontinued. A log file specifying probe temperature at every 2 seconds can be downloaded to a PC after stimulation to confirm that the device has operated as expected and that the participant has actually undertaken the treatment. Given the portable nature of the stimulation device (and the EEG recording apparatus), all stimulation and data acquisition can be performed at bedside by the patient, a carer or therapist.

3.1 Stimulation Settings

<u>The following parameters will be set for active treatments using the CVS Device:</u>

A standardized CVS time-varying waveform lasting approximately 20 minutes will be used for all active treatments. Treatments will be administered twice daily. The two daily treatments will be separated by at least one hour. The waveform schedule for active treatment patients will consist of a warm sawtooth delivered to one ear and, to maximize effect, a cold sawtooth delivered simultaneously to the other ear. The warm sawtooth will go from body temperature to 42 °C, and the cold sawtooth will go from body temperature to 17 °C.

<u>The following parameters will be set for the placebo treatments using the CVS Device:</u>

A standardized CVS time-varying waveform lasting approximately 20 minutes will be used for all placebo treatment patients at all study sites. Treatments will be administered twice daily. The two daily treatments will be separated by at least one hour. The waveform schedule for placebo treatment patients will consist of leaving the earpieces unpowered for a ~20-minute period. However, the cooling fans will be on and the patient will have positive indications that a treatment is being delivered.

The Placebo Device will look identical to the Treatment Device and will show, on its screen, a time-varying waveform similar to that for an active treatment. The y-axis of the plot will be labelled "stimulation intensity" and will not list temperature values (the same will be true for the Treatment Device). A patient receiving a placebo treatment will have the sensation of the earpieces creating some pressure in the ear canals and will hear faint noise associated with the cooling fans. Patients may sense a change in temperature, even though the earpieces will remain unpowered. Placebo patients will not undergo material caloric vestibular stimulation since no temperature gradient will be created across the horizontal semicircular canal. (The threshold for therapeutic benefit using CVS has not been established, but even small temperature changes can result in nystagmus. Therefore, it is not possible to reliably define "sub-therapeutic" CVS).

3.2 Stopping criteria

We plan to administer multiple exposures to CVS in order to encourage experience-dependent long-term plastic change (Hoffman et al., 2002). We will study patients for a maximum of 16 weeks allowing for up to 8 weeks of stimulation. Our previous studies suggest that a 16 week protocol is likely to be feasible for patients and carers to commit to without becoming overly burdensome.

The trial will be stopped if the study clinicians (Drs Sakel/Bodani) and the chief investigator (Dr Wilkinson), or the local NHS R&D unit or sponsor, agree that a critical number of AEs have been reported. The trial may also be terminated if participants and their carers fail to comply with the stimulation protocol (2 x stimulation sessions per each day).

4. Study Design

4.1 Design

A prospective, single-blind, efficacy pilot study using a multiple single case approach will be employed. The design of this study has been formulated with the help of a multi-disciplinary team of clinicians, academics and scientific experts all of which have experience using the CVS device and conducting research within health settings.

4.2 Study Schedule

Potential participants will be identified by the key clinician. If the individual fulfils the entry criteria, he or she will be approached by the key clinician who will inform him or her of the aims and nature of the study. If the patient wishes to receive further information then the clinician will inform the team of key researchers, one of who will meet with them to discuss the study in detail and provide them with an information and consent sheet. The individual will have 24-48 hours to decide whether they would like to participate. Where a favourable view is given, the trial will commence approximately 1 week later at the same location. Upon study registration idiopathic participants will be randomly allocated to one of two treatment arms (see below) with a ratio of 1:1 (cohort 1: cohort 2) (see figure 2). Randomisation of condition allocation will be carried out using an online randomizer (www.randomizer.org).

All participants (n= 32) will complete an initial baseline assessment encompassing a range of behavioural and functional skills (executive function, memory, perception, pain, rehabilitative

progress). Physiological functioning will also be captured using EEG/ERP. This baseline will take place during the first week of enrolment and will then be repeated again during week 4 in order to measure the rate of any spontaneous recovery. We will also perform a video recording of mobility and any other assessments that show impairment at baseline and at the end of the study protocol for comparative reasons.

Cohort one (n=16) will then proceed to the active phase of stimulation whereby CVS will be administered by a staff member or carer (depending on their circumstance) twice a day for 20 minutes, 7 days a week. The CVS device will be pre-set to fluctuate between cold (17°) and warm temperatures (42°) thereby activating the vestibular system. Cohort two (n=16) will instead complete a placebo arm for the duration of the study protocol. During this phase the CVS device will be fitted as normal but the earpieces will remain unpowered, which does not activate the vestibular structures.

Every four weeks, participants will be assessed on the core symptoms of interest. Their physiological activity will also be measured using EEG and heart rate variability (HRV), the latter of which can be simply recorded from one of the EEG electrodes. At the end of the treatment protocol the full baseline assessment will be repeated. 4 weeks post-intervention, the full baseline assessment will once again be repeated to assess carryover.

4.3 Allocation and Binding

Paricipants who fit eligibility will be assigned to one of two groups (cohort 1 vs. cohort 2) randomly using an online randomizer (www.randomizer.org). Treatment allocation will be single-blind. To ensure compliance participants will not be informed of their allocation, and a pre-set stimulation protocol will be programmed onto their CVS machines.

4.4 Outcome Measures

Responsiveness to CVS will be measured using both behavioural and electrophysiological measures (detailed below). A variety of behavioural measures will be included to capture changes in the diverse array of symptoms patients present with. Physiological measures will also be used to monitor brain activity and more subtle changes in various physical functions and cognitive processes.

Behavioural: PD symptoms will be assessed using a neuropsychological test battery composed of standardised measures designed specifically for PD such as UPDRS and PDQ-39 and questionnaires that probe a variety of processes associated with motor skills and abilities

(inc. 2 Minute Walk, 10 Meter Walk and Timed Up and Go), memory (inc. MoCA); cognition (inc. Mini-Mental State Examination); mood (inc. HADS depression and anxiety); and fatigue/sleep disturbance (inc. Fatigue Severity Scale, Epworth Sleepiness Scale). More generalised benefits and activities of daily living will be assessed using measures such as the EQ5D3L and the Schwab and England Scale.

The behavioural measures will be administered at the two baseline assessments (week 1 and 4) and at the end of the treatment/placebo phases. A sample of the measures will also be administered during the interim monthly assessments and follow-up (weeks 8, 12 and 16).

ERP/EEG analysis: EEG abnormalities in PD are most prominently characterised by slower background activity (Neufeld, et al. 1998; Pin, et al. 1992) and changes of the alpha/theta index (Soikkeeli, et al. 1991). PD is also associated with a reduced and slower P300 response to auditory oddball stimuli. We will record these electrophysiological markers to help identify mechanism of effect and lend a degree of objectivity to the more subjective behavioural assessments. We will also analyse power within the main EEG frequency bands and record heart rate variability during the EEG sessions. EEG/ERP will be recorded at baseline and post-stimulation.

5. Study Participants

5.1 Inclusion and Exclusion Criteria

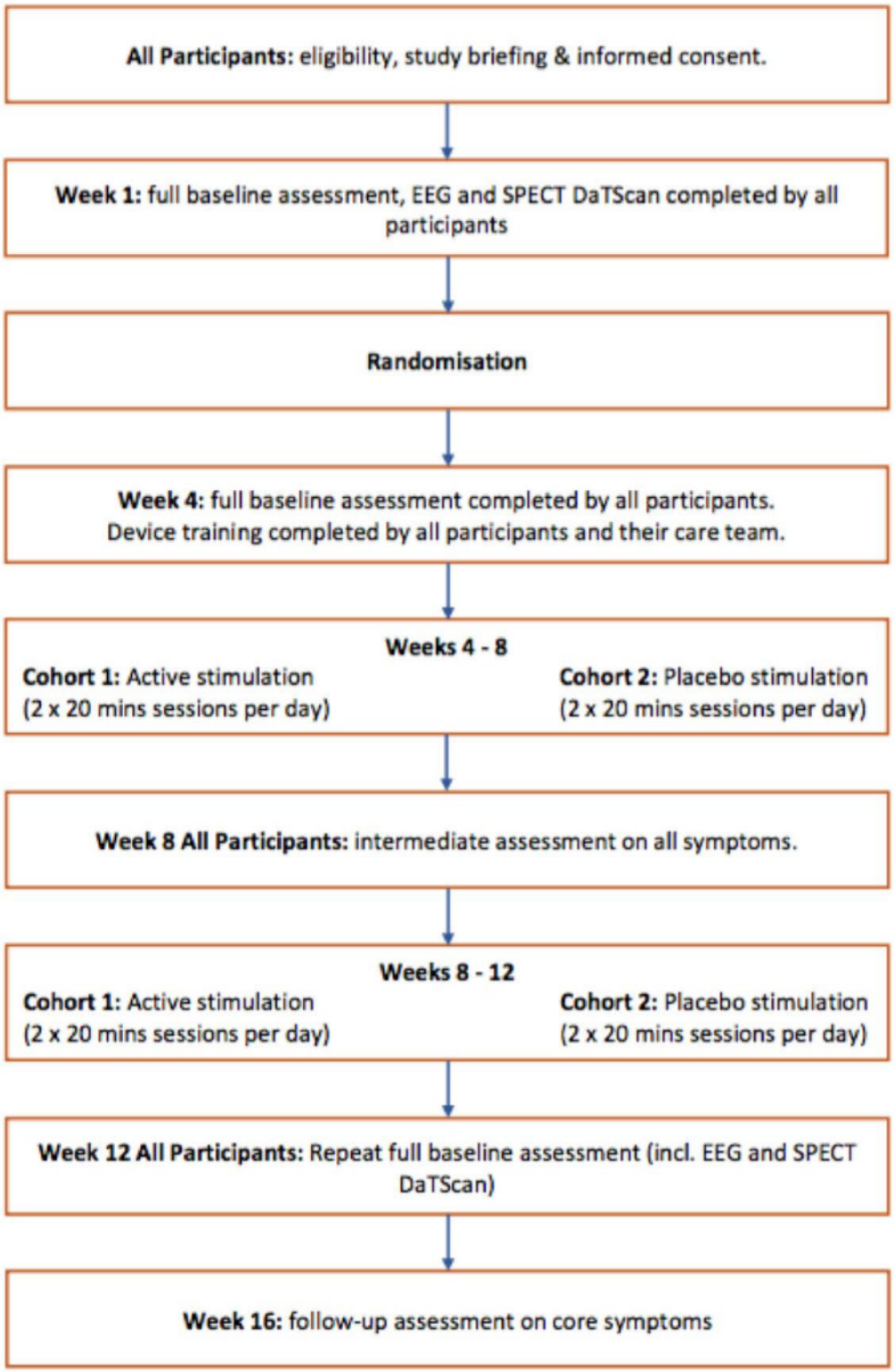
A broad inclusion criteria will be implemented to maximise the generalizability of our findings to PD populations and to facilitate study recruitment processes. These are that:

- Participants must be diagnosed with idiopathic Parkinson's Disease as defined by the UK PDS Brain Bank Criteria.
- Participants must report limitations to Activities of Daily Life (ADL, UPDRS subscale 2)
- Capacity to consent to the study
- Motivated to comply with the protocol
- An understanding of English sufficient to comply with the protocol
- Spouse/ carer willing to support the participant throughout the study

Exclusion Criteria:

- Diagnosis of induced Parkinson's or essential/dystonic tremor
- Premorbid psychiatric history (including affective disorder, psychosis or deliberate self-harm)
- Previous exposure to neurostimulation
- Inner ear pathology

Participant Test Schedule



Demographic data obtained from the participating institutions suggest that approximately 95% of the sample will be white British, 5% will be Asian, and a maximum of 1% will be black, Hispanic or from any

other ethnic or racial category. We will nevertheless continue to actively encourage all minority participants. We do not expect systematic differences in our results as a function of these factors. We point out that as this is a prospective study it is impossible to know in advance the exact proportion of eligible individuals who will be either female or from an ethnic minority.

5.2 Sample Size and Anticipated Effect

We will recruit individuals receiving PD care from the West or East Kent Neuro-rehabilitation, psychiatry, or allied services referred to study by the participating clinicians, Drs Mohamed Sakel, and Mayur Bodani. Using the attached flyer, we will also advertise for participants through the local branch of *Parkinson's UK* – participants from our previous pilot were successfully recruited through this means. The flyer will be distributed via the local branch's email list and also posted on their website.

For all study participants, a letter will be sent to their GP informing him/her of his/her patients' involvement.

As this is a pilot study aiming to establish potential effect sizes that in turn will power a subsequent, more definitive efficacy study, no formal sample size calculation has been performed, however, comparable intervention studies in the literature report statistically significant effects with sample sizes of this magnitude. We estimate a total of 40 participants will be recruited with the expectation that 32 patients and their carers will comply with both the intervention and follow-up.

6. Analysis

6.1 Plan and Statistical Considerations

Comparisons of scores on the behavioural measures in active and inactive (active, placebo) patients will be completed using formal parametric / nonparametric repeated measures tests. The results will be presented as group means (idiopathic cohort 1 and 2) with corresponding confidence intervals. Tests for assumptions will be conducted prior to analysis. For the electrophysiological measures, ANOVA will be used to compare elements of the ERP and more global aspects of the EEG across alternating blocks of active and sham stimulation.

If the active group is shown to be statistically superior to the placebo group then those in the placebo group will be offered the active treatment at the end of study. If there is evidence, as determined by the independent statistician, that a more prolonged treatment schedule may confer greater benefit then the placebo group will be offered the opportunity to receive 4 months of active treatment instead of the current 2. Regardless of whether 2 or 4 months of treatment is received, participants will repeat the assessment schedule that they completed during their earlier treatment phase, with the exception of EEG which given its time-consuming and burdensome nature will be dropped.

Adverse events, general concerns, dropouts and satisfaction will be presented as summary statistics for each group.

6.2 Study end-points

7.2 Track Record of Project Team

-Dr. D. Wilkinson (PI) is a cognitive neuropsychologist with expertise in the cognitive and biological bases of cognitive disorders, including other neurological impairments such as hemi-spatial neglect. His vestibular stimulation laboratory is one of only several world-wide to have investigated the effects of vestibular stimulation in neurological patients. He will have overall responsibility for experimental methodology, day-to-day running of the study, data interpretation and theoretical development.

-Dr. M. Sakel (co-inv and clinical lead) is a Consultant Physician and Director of the East Kent Neuro-Rehabilitation Service, and will refer participants for study and provide clinical input on the design, implementation (inc. assessment of adverse effects) and analyses/interpretation. -Dr. M. Bodani (co-inv) is a Consultant Neuropsychiatrist and directs the NHS neuropsychiatry service across Kent. He will refer participants for study and provide clinical input on the design, implementation and analyses/interpretation.

- Miss A Podlewska (MSc student): Will help deliver the intervention and conduct outcome measurement, as well as data coding and entry, participant recruitment, appointment scheduling, transport arrangement, ordering of supplies, liaison with ethics and governance, report and manuscript preparation, dissemination. Aleksandra has a bachelor's degree in Psychology and has previously worked in neurorehabilitation and neuropsychiatry settings, performing patient testing and evaluation in a number of neurological populations, including those who have suffered from PD. Aleksandra will be assisted by an undergraduate research student.
-Dr J. O'Keeffe qraduated with a bachelor's degree in medicine and surgery (MBBS) in 1998 and is currently CEO of *Machine Medicine* which develops software algorithms to analyse motor dysfunction from patient video. Dr O'Keefe will use this technology to help us characterize any changes in motor function post-treatment that are evident in the video footage collected from our study participants.

8. Physical Infrastructure

The stimulation intervention will be delivered within the patient's home in the community with the support of a carer. Stimulation can also be administered within the School of Psychology at the University of Kent. Other assessments will be performed at the participants' homes or University (depending on their preference).

9. Study Management

9.1 Analysis of Risk/ Benefit

We have previously conducted three NRES REC approved studies that have applied CVS (via the device described above) to neurological patients. Two of these studies have focused on patients with severe traumatic brain injury (in one study these patients were too disabled to self-consent): (i) Rec Ref: 14/EE/1041; An Initial Investigation into the Utility of Caloric Vestibular

Stimulation as a Treatment in Traumatic Brain Injury, and (ii) Rec Ref: 12/LO/0492 Does Vestibular Stimulation Aid Recovery From Low Awareness State? The third study (Rec Ref: 12/LO/1354 A non-invasive neuro-modulation device for migraine headache) focused on episodic migraine. All three studies utilized a similar treatment and assessment protocol to that proposed here and have not reported any serious events or reactions that could be associated with the study.

As noted previously, the aims of this Study involve the mitigation of neuropsychiatric symptoms in the PD subject population. Given the limited options available to the subjects who will be enrolled in the Study, improvement in their overall symptom burden will be viewed as significant. The CVS device is subject to the risks outlined below.

(1) Biocompatibility/toxicity

Biocompatibility is believed to be a minimal risk based on the selection and use of well-characterized materials. In addition, biocompatibility of the aluminum earpieces will be assessed in accordance with the requirements of ISO 10993.

(2) Infection control

Users are instructed to clean the device frequently (the earpieces and the surfaces touching the skin). The users are instructed to use 70% isopropyl alcohol wipes. This cleaning procedure will be independently validated.

(3) Side-effects

Adverse events associated with the application of CVS:

- The risk associated with the use of the CVS device is anticipated to be minimal (classified by the FDA for us in migraine as 'non-significant). Mild nausea, dizziness and drowsiness are hallmarks of activation of the vestibular system, represent anticipated responses to this therapy and thus are not regarded as unanticipated side effects or AEs. The intensity of these symptoms is dose-dependent and reversible with discontinuation of the thermal stimulus. These symptoms typically resolve within 5-10 minutes after the discontinuation of stimulation.

- The primary, low-probability risks associated with use of the device include ear canal irritation and activation of Arnold's nerve with associated cough reflex. Ear canal irritation, if present, should resolve within several hours after the therapy has been discontinued.

- To date, studies conducted by the chief investigator have experienced no unanticipated or serious side effects with the use of the CVS device.

- The device is not an implantable device or for use in supporting or sustaining human life. While it is planned for treatment of PD symptoms, it is transcutaneous and not expected to represent a potential for serious risk to the health, safety, or welfare of a subject. The risks of use of the CVS device are similar to or the same as those experienced when using CVS for vestibular function testing of a patient's body balance system.

- In a review of the guidance document, "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Significant Risk and Non-significant Risk Medical Device Studies: January 2006", the list of non-significant risk devices includes devices with similar characteristics and functions to the device that we will use, such as: (1) Functional non-invasive electrical neuromuscular stimulators, (2) Low power lasers for treatment of pain, and (3) Transcutaneous electric nerve stimulation (TENS) devices for treatment of pain other than angina/chest pain.

(4) Software malfunction

The software for the device has been validated by an independent software engineering firm in accordance with FDA's guidance, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices: May 11, 2005". This guidance has been used for establishing the software level of concern and the developmental documentation requirements, as well as for determining the appropriate verification and validation testing.

(5) Home Use

The PD study plans to permit both "in-clinic" and "at-home" use of the device following an initial training session conducted with the patient and their carer under the supervision of the study team. If after the training session the Study coordinator concludes that the subject is ready, the subject will then be allowed to continue twice-daily treatments at home until the end of the treatment period. The patient will be instructed that if she or he has any questions or encounters any issues at home, the patient should immediately call the Study coordinator. If the Study coordinator concludes that the patient is not ready for self-treating at home and that additional training is needed, the patient will be instructed to return to the clinic the next day (when possible) to receive such additional training.

The device contains software features that allow physician control of the patient-specific treatment: controlling application time, temperature, waveform, and number of treatments. Safety lockouts prevent over-use by patients by limiting the prescription and the number of applications per day. Throughout the study, patients are required to complete interim assessments for continued evaluations and monitoring.

9.2 Monitoring of Research

The safety of this study will be regularly reviewed by the research team who will examine the specific study protocol, assess its risks and benefits, interpret the data, and assure that the study is conducted in the safest and most effective manner.

Although the proposed procedure is associated with minimal risk to subjects, the research team will regularly convene to monitor safety by reviewing AE reports and making future recommendations regarding appropriate safety procedures and proper use and interpretation of data to assure that subject participation is worthwhile.

9.2A Adverse Events

An AE includes any noxious, pathological or unintended change in neurological or bodily function as indicated by physical signs that occurs during the trial, regardless of whether it appears related or unrelated to the treatment.

All AEs will be graded for severity using the following criteria: Grade 0 = (none); Grade 1 = mild: No effect on activities of daily living; Grade 2 = moderate: partial limitation in activities of daily living; Grade 3 = severe: considerable limitation in activities of daily living–medical evaluation required. All AEs will be recorded by the patient and their carer/ care team on an individual diary card or directly to a member of the research team who will record the event using an AE form. A serious adverse event (SAE) is an AE that meets one of the following conditions: death, life–threatening situation (i.e. seizure), hospitalization, severe disruption of daily activity. If an SAE occurs during testing then immediate medical attention will be given from medical personnel at the on–site hospital facilities or by a qualified first–aider. Assessment and monitoring of AEs that occur between sessions will be based on verbal report by the patients and their carers. Patients and their carers will be given contact details so that they are able to report an AE to the research team at any time.

All AEs will be recorded using AE forms which will bear the subjects ID number and will remain on their secure electronic file visible to all members of the research team.

9.2B Discontinued Subjects

Subjects may be discontinued if they fail to meet the requirements of the protocol or meet one of the withdrawal criteria specified above. Patients are expected to complete two daily sessions of stimulation (an hour apart) and attend regular assessments. If participants fail to meet these expectations the chief investigator will review the patient's records and decide whether termination of their participation is required.

Discontinued subjects will be replaced until the study has met its participant quotient.

9.2C Process of Review

The research team will meet in person if required. We will provide summary tables categorizing and reporting the frequency of AEs. We will also compile and present data on the number, gender and ethnicity of subjects. We will summarize on the number of dropouts from the study, and the reason for withdrawal.

9.2D Committee Report and Compliance with Recommendations

After each meeting, the chairperson of the research team will prepare a summary of their meeting with appropriate recommendations. The report will be distributed amongst the team and the R&D departments of the participating trusts.

9.3 Data Handling and Record Keeping

The primary patient records will be kept as completed questionnaires/reports. When in paper format, these records (de-identified) will be scanned, converted to PDF and uploaded onto a secure web-based system (21 CFR part 11 compliant). Data from the electronic measures will also be stored on this system.

All printed and electronic documentation of enrolled participants will bear the patient's unique ID number (assigned at enrolment) as opposed to their name. A name sheet that connects each trial number to each participant will be kept on a physically separate electronic database.

Printed materials obtained from the various tests and other printed source documentation will be kept in locked filing cabinets in the CI's office. Electronic data collected will be entered, in encrypted format, into a password-protected database by a research team member using a dedicated desktop computer.

An electronic screening log will be kept by the study co-ordinator of all referrals (gender, age, ethnic and racial category), including the number of patients who are initially referred to the study, the number who refuse to be referred, the number who meet eligibility, the number who provide informed consent, and the number who subsequently drop out. The referring physicians will provide information on the number who may meet initial eligibility but refuse to be referred, and the co-ordinator will be responsible for completing all other aspects of the log. No names will be recorded in this log.

All personal data will be handled with extreme care and will adhere to the Data Protection Act and in accordance with MRC guidelines for the handling of personal data.

After final follow-up the Chief Investigator will assume responsibility for maintenance and access to the electronic database and all other data. The Chief Investigator alone will be authorized to make corrections to data and patient records. Researchers will need to contact the Chief Investigator for any data queries or to request an amendment.

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Annex 1: Schedule of Events for idiopathic group

Enrolment/Screening	• *Informed Consent* • *If enrolled, complete Screening Visit form* • *If meet criteria complete participant questionnaire* • *Arrange initial baseline assessment* •*Arrange training session with CVS device*
Days 1-4 (up to 4) in patient's home	• *Day 1/ 2- Device training session given to patient and their carer* • *Day 3/4 - Administer full baseline assessment*
Day 28: Subject repeats baseline	• *The full baseline assessment is repeated* • *Subject performs a treatment under observation by a research team member to reconfirm proficiency*
During the Treatment Period (weeks 4-12)	•*A research team member contacts the patient to ensure that she/he is using the Device consistently and making prompt diary entries* •*A monthly assessment of the core symptoms of interest is completed at the patients' home*
Final treatment visit for Subject	• *Complete full baseline assessment* • *Patient returns CVS Device* • *Collect all treatment delivery data from the CVS Device*
Follow-up visit for Subject	•*Complete core assessment* • *Debrief patient and carer* • *Interview patient with regard to CVS Device*