A durable gain in motor and non-motor symptoms of Parkinson's Disease following repeated caloric vestibular stimulation: A single-case study.

David Wilkinson[1], Aleksandra Podlewska[1] & Mohamed Sakel[2].

[1]School of Psychology, University of Kent, Canterbury, Kent, CT2 7NP, UK.
[2]East Kent Neuro-Rehabilitation Service, East Kent Hospitals University NHS Foundation Trust, Kent, CT1 3NG, UK.

Correspondence to David Wilkinson: Tel +44 (0)1227 824772. Fax: +44 (0)1227 8247030. Email: dtw@kent.ac.uk

Abstract

Objective: To gain 'first-in-man' evidence that repeated caloric vestibular stimulation (CVS), a non-invasive form of neuro-modulation, can induce a lasting and clinically-relevant reduction in Parkinson's Disease (PD) symptoms.

Methods: A 70yr old male, diagnosed with PD 7 years prior to study enrolment, self-administered CVS at home 2x20 minutes per day for three months using a solid-state portable device. Standardised neuropsychological assessments of motor, cognitive, affective and independent function were carried out prior to stimulation, at the start and end of the sham (month 1) and active (months 2-3) phases, and 5 months post-stimulation.

Results: Relative to the pre-stimulation baseline, behavioural improvements that exceeded the minimal detectable change were observed on the EQ5D, Unified Parkinson's Disease Rating Scale, Schwab and England scale, 2 minute walk, Timed up and go, Non-motor symptom assessment scale for PD, Montreal cognitive assessment, Hospital depression scale and Epworth sleepiness scale. The level of change exceeded the threshold for a minimal clinically important difference on all scales for which a threshold has been published. By contrast, little improvement was seen during the sham (i.e. placebo) phase.

Conclusion: Caloric vestibular stimulation may offer a novel, home-based method of relieving everyday symptoms of PD, and merits further evaluative study.

Introduction

The vestibular system detects linear, angular and gravitational acceleration of the head and plays an important role in the autonomic control of eye movement, posture, gait and egocentric perception (see Smith & Zheng, 2013). Artificial stimulation of the peripheral balance organs, via either galvanic or thermal current, up-regulates metabolic activity across a range of cortical, striatal and cerebellar brain areas (Lopez, Blanke & Mast, 2012). The clinical relevance of this metabolic activity has been demonstrated in a number of acquired neurological conditions including hemi-spatial neglect (Wilkinson et al., 2014), aphasia (Wilkinson, Morris, Milberg & Sakel, 2013), mania (Levine et al., 2012), central pain (McGeoch, Williams, Lee & Ramachandran, 2008) and post-stroke postural instability (Sturt & Punt, 2013). Despite these promising results, comparably little investigation has been conducted with individuals who suffer from neuro-degenerative disease.

Recent study has, however, produced growing theoretical interest in the idea that ascending projections from the vestibular brainstem nuclei may provide a 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 reticulata (Samoudi, Nissbrandt, Dutia & Bergquist, 2012). In human PD studies, galvanic vestibular stimulation has been shown to spontaneously reduce postural sway (Pal, Rosengren & Colebatch, 2009), postural response time (Samoudi, Jivegård, Mulavara, & Bergquist, 2015) and also lead to a quickening of bradykinesic rest-to-active transitions in the wrist and trunk (Pan, Soma, Yamamoto, 2008). Although these results demonstrate the potential therapeutic value of vestibular stimulation in PD, they 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. In this brief report, we provide the first evidence, drawn from a single-case study, that repeated sessions of vestibular stimulation can induce durable, clinically meaningful improvements in both the motor and non-motor symptoms of PD.

Participant

The participant, a male, aged 70yrs, was diagnosed with PD 7years prior to study enrolment. At study screening, his predominant symptoms were hypokinesia, rigidity and memory loss although formal testing revealed a far broader range of motor and cognitive difficulties – see baseline data in Table 1. His medication (stalevo 150mg/25mg/200mg, levodopa 100mg with carbidopa 25mg and entacapone 200mg tablets 3 times per day; pramipexole dihydrochloride 1mg tablets 3 times per day) remained unchanged throughout the study.

Intervention

Vestibular stimulation was induced using a novel, caloric device (*Scion Neurostim*) comprising a headset fashioned like music headphones with aluminum earpieces that contained a solid-state heater/cooler element which warmed and cooled the external ear canals via controlled, time-varying thermal waveforms (see Figure 1). One earpiece delivered a cold sawtooth waveform (ear canal temperature to 17^0C every 2mins) and the other delivered a warm sawtooth (ear canal temperature to 42^0C every 1 minute). To ensure balanced hemispheric activation over the course of the study (warm currents primarily activate ipsilateral cortex while cold currents primarily

activate contralateral cortex) we switched the waveform assigned to each ear every 2 days. Each stimulation session lasted 20mins during which time the patient lay passively supine with his head resting on a wedge-shaped pillow angled at 30^0. Two sessions, spaced at least 4hrs apart, were administered by the patient (with the help of his wife) twice per day, 5 days per week for 3 months. Sham stimulation was delivered in the first month, followed by 2 months of active stimulation. In the sham condition, the unit was operated in the same way as in the active condition, but no power was delivered to the earpieces. The patient was informed that various doses would be administered over the 3 months, and that although there may be times when temperature changes could be felt in the ear (i.e. in the active condition), this should not be taken as evidence that the device was now any more or less effective.

Following institutional ethics approval and the patient's informed consent, standardised clinical outcome measures with high test-retest reliability and sensitive to both motor (Unified Parkinson's Disease Rating Motor sub-scale; 2 minute Walk, Timed up and go) and non-motor symptoms (Unified Parkinson's Disease Rating ADL sub-scale, Non-motor symptom assessment scale, Montreal cognitive assessment, Epworth sleepiness scale, fatigue severity scale) and more general well-being and functional capacity (Schwab and England scale, Hospital anxiety and depression scales, EQ5D) were administered in random order 2 weeks prior to sham stimulation, at the end of the 4 week sham block, at the end of the 1st and 2nd active months, and then at 5 months follow-up after stimulation.

Figure 1 about here

Results

As can be seen in Table 1, improvement was observed across nearly all measures during the active relative to sham phase; mobility and cognition increased

dramatically and the patient reported feeling less anxious and able to sleep better. Consistent with a cumulative effect, the greatest improvement was typically observed during the second month of active stimulation, and was still evident at 5months follow-up. These improvements were too large to attribute to published measurement error and exceeded the statistical criterion for minimal clinically important change (MCID) on the UPDRS motor and ADL sub-scales, Schwab & England ADL scale, and HADS depression scale (MCID criteria were unavailable for the other tests).

Table 1 here

Discussion

The favorable outcome in this individual could in theory be explained by coincident change unrelated to the intervention, however both the consistency and scale of change and the fact that it was time-locked to the transition from sham to active stimulation makes this less likely. Although the individual was led to believe that thermal sensations in his ear should not be taken as evidence that the stimulation was now somehow more effective, it is conceivable that the sensation uniquely associated with active stimulation improved his behavioural performance via psychological (i.e. placebo-based), as opposed to neurological, means. It is, however, difficult to believe that an improvement of this origin would still be evident at both formal assessment and from relatives' testimony 5months later. In line with previous study (Samoudi et al., 2012, 2015), we therefore tentatively attribute the effects to a vestibular-based mechanism.

As highlighted by Benninger and Hallett (2015), the shortcomings of conventional pharmacological therapy coupled with the recent success of deep brain stimulation in advanced PD has raised interest in non-invasive forms of neuro-

stimulation, however, there has so far been little evidence from transcranial studies that the reported gains translate to long-lasting improvements in well-being and functional independence. We recognize that the inferential power of the present single-case study is limited, however, the improved response profile demonstrated by the participant, perhaps most notably at 5months follow-up, alludes to a practical patient benefit that, in our opinion, justifies larger-scale investigation. Although the biological basis of recovery was not investigated here, we speculate that the non-motor gains point to activation of non-dopaminergic pathways and may underline the growing therapeutic relevance of the pedunculopontine nucleus given that it both sends and receives dense projections from areas with known vestibular responses and, when directly activated via deep brain stimulation, has been associated with heightened cognition and arousal (Ballanger et al., 2009).

Finally, we note that the potential of CVS to help treat cognitive and motor dysfunction in both acquired and dementing neurological illnesses has long been discussed, however, widespread investigation has been hampered by the reliance on cold-water irrigation of the external ear canal which induces nausea and dizziness and is unsuited for repeated administration. Recent advances in biomedical engineering have, however, led to the development of home-use, solid-state devices which enable the temperature of the waveform to be both varied and tightly controlled which in turn offsets physiological habituation and allows the temperature to be maintained at or above 15^0C. This temperature is too mild to induce distracting side-effects but is the approximate point at which the vestibular nerves reach asymptote (Reker, 1977). These technical developments have enabled CVS to become a tool that is potentially relevant to the management of PD and, given the data reported here, should motivate investigations that move beyond single-case and small-group designs.

Declaration of Interest

The authors have no competing interests to declare.

Acknowledgements

We are grateful to the participant for his co-operation and effort, and thank Scion Neurostim for providing the caloric vestibular stimulation device.

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	Baseline	*Sham*	*Active 1*	*Active 2*	*Follow-up*
EQ5D					
mobility	2	2	2	2	2
self-care	2	2	2	2	2
usual activities	2	2	2	2	2
pain/discomfort	2	2	2	1*§	1§
anxiety/depression	2	2	1§	1§	1§
UPDRS					
total	85	79*	57§	41*§	55§
subscale I	7	6	6	4*§	1*§
subscale II	24	24	17§	12*§	15§
subscale III	54	49*	34§	25*§	39§
Schwab and England (%)	64	65	64	72*§	70§
2minute walk (meters)	22	36	84§	120*§	102§
Timed up and go (secs)	20.4	23	21.5	16.2*§	13.3§
NMSS	109	108	101	49*§	58§
MoCA	12	12	14	21*§	20§
HADS					
depression	11	11	5§	5§	4§
anxiety	4	4	2	0	0
ESS	16	15*	18	8*§	7*§
FSS	5.2	5.4	4.4	4.1	4.2

Abbreviations: *exceeds minimal detectable change (MDC) from preceding score; §exceeds MDC from sham score. UPDRS=Unified Parkinson's Disease rating scale; NMSS=Non-motor symptom assessment scale for Parkinson's Disease; MOCA=Montreal cognitive assessment; HADS=Hospital anxiety and depression scale; ESS=Epworth sleepiness scale; FSS=Fatigue severity scale of sleep disorders.

Table 1. Patient test scores

Figure caption

Figure 1. Schematic of the headset and hand-held user interface of the thermo neuro-modulation unit used to deliver caloric vestibular stimulation.

Figure 1