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Sasegbon, Ayodele, Hammerbeck, Ulrike , Michou, Emilia, Cheng, Ivy, Zhang, Mengqing, James, Charlotte and Hamdy, Shaheen (2022) A feasibility pilot study of the effects of neurostimulation on swallowing function in Parkinson's Disease [version 2; peer review: 1 approved, 1 approved with reservations, 1 not approved]. AMRC Open Research, 3 (19). ISSN 2517-6900

DOI: <https://doi.org/10.12688/amrcopenres.13007.2>

Publisher: F1000 Research Ltd

Version: Published Version

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Data Access Statement: Figshare. Parkinsons study data AOS.xlsx. DOI: <https://doi.org/10.48420/14958540.v1>

This project contains the following data:

- Data from a feasibility pilot study of the effects of neurostimulation on dysphagia recovery in Parkinson's Disease

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC BY 4.0 Public domain dedication).

Figshare. Study Protocol: Exploring Novel Neurostimulation Based Therapies for Swallowing Impairments in Parkinson's Disease. DOI: <https://doi.org/10.48420/14995077.v1>

Figshare. CONSORT checklist for study "A feasibility pilot randomised controlled study of the effects of neurostimulation on dysphagia recovery in Parkinson's Disease" DOI: <https://doi.org/10.48420/15082662.v1>

Figshare. CONSORT flowchart for the study "A feasibility pilot randomised controlled study of the effects of neurostimulation on dysphagia recovery in Parkinson's Disease". DOI: <https://doi.org/10.48420/15082674.v2>

Enquiries:




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RESEARCH ARTICLE

REVISED **A feasibility pilot study of the effects of neurostimulation on swallowing function in Parkinson's Disease [version 2; peer review: 1 approved, 1 approved with reservations, 1 not approved]**

Previously titled 'A feasibility pilot study of the effects of neurostimulation on dysphagia recovery in Parkinson's Disease'

Ayodele Sasegbon ¹, Ulrike Hammerbeck ¹, Emilia Michou ^{1,2}, Ivy Cheng ¹, Mengqing Zhang¹, Charlotte James¹, Shaheen Hamdy ¹

¹Division of Diabetes, Endocrinology and Gastroenterology, University of Manchester, Manchester, Greater Manchester, Stott Lane, Salford M6 8HD, UK

²Department of Speech and Language Therapy, University of Patras, Patras, Greece

v2 First published: 01 Sep 2021, 3:19
<https://doi.org/10.12688/amrcopenres.13007.1>
 Latest published: 08 Apr 2022, 3:19
<https://doi.org/10.12688/amrcopenres.13007.2>

Abstract




Introduction: Dysphagia often occurs during Parkinson's disease (PD) and can have severe consequences. Recently, neuromodulatory techniques have been used to treat neurogenic dysphagia. Here we aimed to compare the neurophysiological and swallowing effects of three different types of neurostimulation, 5 Hertz (Hz) repetitive transcranial magnetic stimulation (rTMS), 1 Hz rTMS and pharyngeal electrical stimulation (PES) in patients with PD.



Method: 12 PD patients with dysphagia were randomised to receive either 5 Hz rTMS, 1 Hz rTMS, or PES. In a cross-over design, patients were assigned to one intervention and received both real and sham stimulation. Patients received a baseline videofluoroscopic (VFS) assessment of their swallowing, enabling penetration aspiration scores (PAS) to be calculated for: thin fluids, paste, solids and cup drinking. Swallowing timing measurements were also performed on thin fluid swallows only. They then had baseline recordings of motor evoked potentials (MEPs) from both pharyngeal and (as a control) abductor pollicis brevis (APB) cortical areas using single-pulse TMS. Subsequently, the intervention was administered and post interventional TMS recordings were taken at 0 and 30 minutes followed by a repeat VFS within 60 minutes of intervention.

Results: All interventions were well tolerated. Due to lower than expected recruitment, statistical analysis of the data was not undertaken. However, with respect to PAS swallowing timings and

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	1	2	3
version 2 (revision) 08 Apr 2022			 view
version 1 01 Sep 2021	 view	 view	

1. **Jin Woo Park** , Dongguk University Ilsan Hospital, Gyeonggi-do, South Korea
2. **Corinne A. Jones**, Dell Medical School, The University of Texas at Austin, Austin, USA
The University of Texas at Austin, Austin, USA
3. **Paul Muhle** , University Hospital Muenster, Muenster, Germany

Any reports and responses or comments on the article can be found at the end of the article.

MEP amplitudes, there was small but visible difference in the outcomes between active and sham.

Conclusion: PES, 5 Hz rTMS and 1 Hz rTMS are tolerable interventions in PD related dysphagia. Due to small patient numbers no definitive conclusions could be drawn from the data with respect to individual interventions improving swallowing function and comparative effectiveness between interventions. Larger future studies are needed to further explore the efficacy of these neuromodulatory treatments in Parkinson's Disease associated dysphagia.

Keywords

Dysphagia, Swallowing, rTMS, PES, Parkinson's



This article is included in the [Parkinson's UK](#) gateway.

Corresponding author: Ayodele Sasegbon (ayodele.sasegbon@manchester.ac.uk)

Author roles: **Sasegbon A:** Data Curation, Formal Analysis, Investigation, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Hammerbeck U:** Data Curation, Investigation, Project Administration, Writing – Review & Editing; **Michou E:** Conceptualization, Funding Acquisition, Investigation, Project Administration, Writing – Review & Editing; **Cheng I:** Data Curation, Investigation, Validation, Writing – Review & Editing; **Zhang M:** Data Curation, Investigation, Writing – Review & Editing; **James C:** Investigation; **Hamdy S:** Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing

Competing interests: Shaheen Hamdy is chief scientific officer, a shareholder, and a board member of Phagenesis Ltd., a company that focuses on dysphagia therapies, specifically pharyngeal electrical stimulation. Shaheen Hamdy has also received research funding from MRC, Wellcome Trust, Stroke Association, and NIHR to explore brain stimulation strategies to treat post-stroke dysphagia. All other authors declare no conflicts of interest.

Grant information: Funding for this study was provided by Parkinson's UK (grant reference G-1401).

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How to cite this article: Sasegbon A, Hammerbeck U, Michou E *et al.* **A feasibility pilot study of the effects of neurostimulation on swallowing function in Parkinson's Disease [version 2; peer review: 1 approved, 1 approved with reservations, 1 not approved]** AMRC Open Research 2022, 3:19 <https://doi.org/10.12688/amrcopenres.13007.2>

First published: 01 Sep 2021, 3:19 <https://doi.org/10.12688/amrcopenres.13007.1>

REVISED Amendments from Version 1

The paper has been adjusted in line with the suggestions from the two peer reviewers. Changes include:

- The study title has been changed. It now reads "A feasibility pilot study of the effects of neurostimulation on swallowing function in Parkinson's Disease"
- Further justification in the introduction for using neuromodulation to address dysphagia in Parkinson's Disease (PD)
- Stand-alone aim and hypothesis sections as opposed to these sections being integrated into the text at the end of the introduction
- Changes to the layout of the methods section. These include moving the protocol section, so it appears earlier in the section and minor changes to abbreviations.
- The results section now incorporates text referring to tolerability
- The limitations section of the paper has been expanded to include information stating the penetration aspiration score (PAS) is not without its drawbacks when it comes to assessing swallowing function.

Any further responses from the reviewers can be found at the end of the article

Introduction

Parkinson's disease (PD) is a common neurodegenerative condition of unclear aetiology wherein there is a build-up of Lewy Bodies within dopaminergic regions of the brain¹. These Lewy Bodies are primarily composed of the protein alpha synuclein and cause damage to the internal workings of neurones^{2,3}. As the disease progresses, there is an increasing burden of pathological protein and an associated decline in neuronal function^{1,4,5}. From the point at which a diagnosis of PD is made, patients tend to exhibit an increasing number of symptoms in a predictable manner. As a result, symptomatic scales such as the Hoehn and Yahr scale⁶ are often used to classify PD severity. Epidemiological studies have shown PD is present in up to 4% of people over 55 years of age^{7,8}. Although the limb and gait disturbances caused by PD are common and well known⁵, PD is also recognised to cause dysphagia⁹. Dysphagia commonly occurs in patients with PD¹⁰, with up to 82% of patients developing dysphagia at some point along their illness journey¹¹. PD can cause dysphagia directly or indirectly. The direct pathway occurs as a result of Lewy body related damage to swallowing centres within the brain¹². Conversely, the indirect pathway is due to damage to non-motor brain areas which results in dementia¹³ which in turn causes dysphagia¹⁴.

At present the management of dysphagia in PD is geared towards compensating for neurological damage with interventions such as dietary modification, altering the consistency of fluids and the use of dopaminergic medications^{15,16}. However, a body of evidence exists in support of invasive deep brain stimulation (DBS) for the treatment of PD motor symptoms¹⁷. DBS

delivered to the subthalamic nucleus or globus pallidus is effective at ameliorating motor dysfunction up to 12 months after treatment¹⁷. There is little data on whether DBS can treat PD dysphagia. Beyond this, neuromodulatory interventions constitute new and emerging developments in the treatment of neurogenic dysphagia. Novel and increasing applied techniques include pharyngeal electrical stimulation (PES) and repetitive transcranial magnetic stimulation (rTMS). PES is a technique whereby a catheter containing two electrodes is inserted transnasally or per-orally into the pharynx. The application of an electric current results in stimulation of sensory afferents supplying the pharynx and increased sensory inflow into brain areas including the sensory and motor cortices¹⁸. rTMS, by contrast, is a centrally acting as opposed to a peripherally acting technique. It uses a strong electromagnet to pulse magnetic energy at targeted parts of the brain including the swallowing motor cortical areas¹⁹. High-frequency rTMS (5 Hertz or greater) causes increases in pharyngeal motor cortical neurological excitability²⁰ while low frequency (1 Hertz) rTMS causes a suppressive effect²¹.

In PD the nature of Lewy body deposition, neuronal damage and attempted neuroplastic compensation results in cortical areas with decreased activity²² and others with increased activity²³. Within the areas with decreased activity damage can be said to have exceeded compensatory efforts, while in areas with increased activity attempted compensation is ongoing but with unclear effectiveness. Cortical rTMS and PES have been hypothesised to encourage beneficial neuroplastic changes in the brains of patients with neurogenic dysphagia in two distinct ways. Firstly, high frequency (excitatory rTMS) or PES are excitatory and increase neuronal activity over cortical swallowing centres²⁴. This increase in activity can either reverse suppressed neuronal activity due to pathological damage, thereby restoring a more normal state of activity^{25,26}, or perhaps increase activity in non suppressed areas thereby acting as a trigger to encourage compensation for contralateral damage or restoration of normal activity in areas with disordered neuronal firing. Secondly, low frequency (suppressive rTMS) is thought to block maladaptive neuronal activity in the motor cortex thereby allowing beneficial neuroplastic changes to occur²⁶.

Very few non-invasive neurostimulatory studies have been performed in PD with even fewer being performed in the field of dysphagia. Regarding PES, no study has been performed investigating the effects of PES on PD related dysphagia. However, PES has been used in numerous studies as a treatment for post-stroke dysphagia (PSD)^{27,28}. A meta-analysis of these studies shows PES is able to improve swallowing performance²⁹. Moreover, a single randomised controlled trial utilising high-frequency rTMS in PD dysphagia was performed in 2019 by Khedr *et al.*³⁰. In that study, rTMS was shown to lead to improvements in a functional dysphagia scale (the Arabic dysphagia handicap score) and pharyngeal transit time for thin fluids and solids³⁰. Despite the dearth of rTMS swallowing studies in PD, numerous rTMS studies have been performed in the field of PD limb motor function. While their findings are not directly translatable, they do give an idea

of potential swallowing therapeutic effects. These studies have employed both low (1 Hz) and high frequency (5 Hz) cortical targeted rTMS. A meta-analysis of the motor effects of rTMS has shown low-frequency rTMS is able to improve PD limb symptoms³¹. High-frequency rTMS trended towards but did not achieve significance²⁶.

Hypothesis

We hypothesise that rTMS and PES will improve swallowing function in patients with PD associated dysphagia.

Aims

In patients with dysphagia secondary to PD, we aim to compare the neurophysiological and videofluoroscopic (VFS) swallowing behavioural effects of: Low-frequency rTMS (1Hz), High-frequency rTMS (5Hz) and PES

Objectives

Our objectives were to generate data establishing proof of concept, feasibility, safety and tolerability.

Methods

The study was designed as a triple intervention, two-armed crossover, randomised controlled feasibility trial (Figure 1). Although the initial aim was to recruit 66 participants, the COVID-19 pandemic made this unfeasible. For each of the

three interventions; 1Hz rTMS, 5Hz rTMS and PES, active stimulation was compared with sham. Over the course of the study, each patient was randomly allocated to one of the three interventions and attended the neuro-motility laboratory on two occasions separated by at least one week. During their initial attendance they received either real or sham stimulation and during their second attendance, the alternative.

The study was assessed and granted ethical approval by the Yorkshire & The Humber - Leeds East Research Ethics Committee (17/YH/0031) and registered on ClinicalTrials.gov (NCT03253354).

Patient recruitment

Participants were recruited from general neurology clinics, dedicated PD clinics in Salford Royal Hospital (Salford, UK) and PD UK branch meetings.

Inclusion criteria required that patients be diagnosed with PD at least two years prior to the start of the study. Furthermore, patients needed to complain of symptoms of dysphagia, be able to give informed consent and have moderate to severe PD (Hoehn and Yahr Scale II to IV)⁶.

The study exclusion criteria were designed to remove patients: with non-PD causes of dysphagia, with PD mimicking

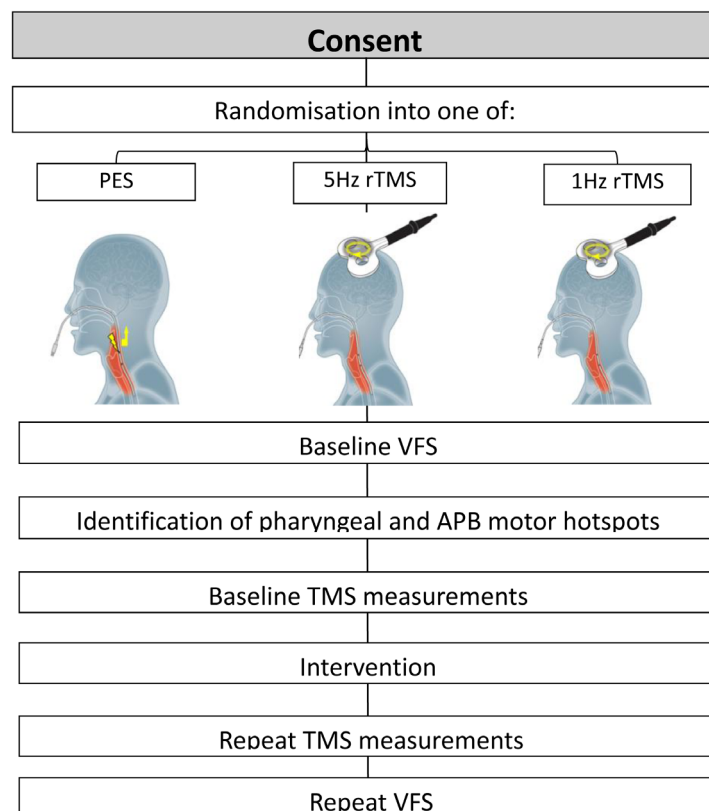


Figure 1. Flowchart illustrating study protocol.

pathologies (multi-system atrophy etc.), lacking capacity to give informed consent and possessing contra-indications for TMS (epilepsy, cardiac pacemakers and metal within the head or neck).

After consenting participants, randomisation to intervention and treatment arms (active or sham) was performed using the statistical website Randola (<http://www.rando.la/>). Participants then received a screening VFS but only progressed into the study if they had a penetration aspiration score (PAS) of 2 or more, indicating swallowing dysfunction. Patients were blinded (so far as possible) to the intervention they received.

Symptomatology and activities of daily living

Following randomisation, researchers spoke to participants and completed a Hoehn and Yahr scale⁶ and Schwab and England activities of daily living (ADL) scale³².

Outcome measures

The primary outcome measure for the study was any change between pre- and post-interventional VFS assessed PAS for barium of a 'thin fluid' consistency. PAS constitutes an effective means of assessing dysphagia in clinical practice and in research³³. Cumulative PAS scores were calculated, for primary and secondary PAS outcome measures (see below) and for each thickness or task of barium sulphate swallowed.

Secondary outcome measures included:

1. Change in PAS scores with paste consistency, solid consistency (biscuit covered with barium sulphate) and cup drinking of thin barium sulphate fluid.
2. Swallowing timing measurements during thin fluid swallowing, including oral transit time (OTT), pharyngeal transit time (PTT) and pharyngeal response time (PRT). OTT was defined as the time from bolus propulsion to its passage past the ramus of the mandible into the pharynx. PTT was defined as the time from passage of the bolus into the pharynx to its passage through the upper oesophageal sphincter. PRT was defined as the time from passage of a bolus into the pharynx to elevation of the hyoid.
3. Change in pharyngeal motor evoked potential (PMEP) amplitudes (see study procedures below). Changes in PMEP amplitudes have been shown by previous studies in the field to be correlated with changes in neuronal excitability within the swallowing motor cortex³⁴.

Study protocol

During each session, patients were first taken to the videofluoroscopy (VFS) suite for measurements of their PAS swallowing baseline. Subsequently, they were escorted to the neurophysiology laboratory and seated in a chair. A disposable surgical cap was placed over their heads and secured with medical tape. The location of their cranial vertex was then identified and marked as has been described in previous studies³⁵. Abductor pollicis brevis (APB) electrodes and an

intraluminal pharyngeal catheter were then positioned. Following this, single-pulse TMS was used to locate pharyngeal motor cortical hotspots bilaterally and the APB motor cortical hotspot on the hemisphere with the lowest pharyngeal resting motor threshold (RMT). RMTs over pharyngeal and APB areas were determined as has been described in previous studies³⁶.

Baseline PMEP and APB MEP measurements were obtained by delivering 10 pulses of single-pulse TMS over pharyngeal motor areas bilaterally and the APB area over the 'dominant' pharyngeal hemisphere. Following this, either real or sham: 1 Hz rTMS, 5 Hz rTMS or PES was administered. Repeat MEP measurements were then obtained immediately after the intervention and 30 minutes after the intervention. Lastly, participants were taken to the VFS suite for a repeat set of swallowing measurements. A flow chart of the key points of the study protocol can be seen in [Figure 1](#).

Study procedures

Electromyography. Electromyography EMG recordings (allowing measurements of motor evoked potentials) were obtained from the pharynx and the abductor pollicis brevis (APB). Pharyngeal recordings were made using a trans-nasally inserted intraluminal catheter (Gaeltec, Isle of Skye, UK) as described before³⁷. APB EMG signals for recording APB MEPs were used as a control and acquired as previously reported³⁶.

Videofluoroscopy. VFS recordings were obtained with the assistance of trained radiographers. Participants were seated following which the X-ray source and detector were positioned such that lateral views of oropharyngeal structures could be obtained. Images were recorded continuously at 30 frames per second.

Participants were then asked to swallow 10 thin liquid boluses with a volume of 5 ml (barium sulphate w/v ratio of 60%, equivalent to a IDDSI value of 0). Subsequently, they were asked to swallow 3 boluses of a paste consistency (w/v ratio of 40% achieved with 'Resource Thicken Up Clear' (Nestle, UK), the equivalent of IDDSI 3) and 3 solid swallows (IDDSI 7). Finally, participants were asked to drink two 50 ml aliquots of thin liquid (IDDSI 0). Barium sulphate (E-Z-Paque, UK) was mixed with water or spread over the surface of solids so as to enable VFS visualisation of boluses. Participants' VFS PAS data were analysed by a speech therapist blinded to the group assignment. PAS values were obtained for every primary and secondary clearing swallow performed. A primary swallow was defined as the first swallow performed when a bolus was ingested, while secondary or clearing swallows were the subsequent swallow that participants performed to clear any residue. Swallowing timing measurements for thin fluid swallows (OTT, PTT and PTR) were also performed by the same blinded speech and language therapist (IC).

During each study session, participants had baseline and post-interventional VFS recordings. As a safety feature of the study, VFS was stopped if a participant was noted to aspirate

more than 50% of bolus volume on 3 consecutive swallows (3 consecutive PAS scores of 8).

Single-pulse transcranial magnetic stimulation. Single-pulse TMS was used to elicit motor evoked potentials (MEPs) from pharyngeal and APB motor cortical hotspots. Pulses were delivered using a figure-of-eight electromagnetic coil 7 cm in diameter, with a field strength of 2.2 Tesla, connected to a Magstim Bistim Unit (Magstim, Whitland, UK).

When in use, the coil was held flat against a disposable surgical cap placed over a participant's head at an angle of 45 degrees. Motor mapping was performed as has been described in several published studies^{37,38}. Single-pulse TMS was also used to measure PMEP and APB MEP amplitudes. This was done by delivering 10 pulses of stimulation at 120% of the resting motor threshold (RMT) of the pharyngeal or APB motor areas being studied.

Pharyngeal electrical stimulation. PES was delivered using a 3.2mm intraluminal catheter (Gaeltec, Isle of Skye, UK) positioned within the pharynx. The catheter was connected to a signal generator (Digitimer model DS7, Hertfordshire, UK) and a trigger generator (Digitimer Neurology system, Hertfordshire, UK)³⁹.

Electrical stimulation was delivered at an intensity determined by the patient's initial sensory threshold and maximum tolerated sensory threshold. The initial sensory threshold was defined as the intensity of electrical stimulation at which a participant first feels they are being stimulated. The maximum tolerated sensory threshold was defined as the electrical intensity at which patients experienced discomfort. To establish these two thresholds the signal generator current was increased in increments of approximately 0.1mA each second until patients stated that they could feel a sensation in their throat. The intensity at which this occurred was noted and the process repeated twice more. The mean of the three values was then calculated. The maximum tolerated intensity was determined by increasing the electrical intensity further until patients stated that it felt uncomfortable. The intensity of pharyngeal stimulation was set at 75% of the difference between the two values³⁹.

Active PES was delivered at a frequency of 5Hz for 10 minutes³⁹. For sham PES, the intraluminal catheter was inserted but no electrical stimulation was delivered.

Repetitive transcranial magnetic stimulation. RTMS was performed using a Magstim super rapid generator (Magstim, Whitland, UK) connected to a 7cm figure-of-eight coil. High-frequency excitatory rTMS was performed by positioning the coil over the pharyngeal motor cortical area with the lowest RMT (the 'dominant' swallowing hemisphere) and delivering 250 pulses at 5 Hz at an intensity of 90% of RMT²⁸. Low-frequency suppressive rTMS was also delivered over the pharyngeal motor cortical area, again with the lowest RMT, 600 pulses at a frequency of 1 Hz and an intensity of 120%

RMT²⁴. Sham rTMS was delivered using the coil tilt technique³⁵ where the subject could feel the coil on their scalp and noise of the stimuli, but no energy was delivered to the brain beneath.

Data analysis

As this study was intended to be a small pilot study exploring the feasibility of using neurostimulatory techniques to induce beneficial changes in swallowing function, only descriptive statistics including means, medians and standard deviations (SD), were used to compare each active treatment (5 Hz rTMS, PES and 1 Hz rTMS) to sham. Hoehn and Yahr and Schwab and England ADL scores were also compared between groups.

Penetration aspiration scores. The PAS with the highest numerical value was recorded for each swallow before being added together for each category (thin fluid, paste, solid and cup drinking) to give cumulative penetration aspiration scores²⁸. Cumulative scores were converted into percentage differences from individual baseline.

Swallowing timing measurements. OTT, PTT and PRT values were obtained from VFS recordings for all interventions for thin fluid swallows before being converted into percentage changes from baseline.

Motor evoked potentials. MEP amplitudes were measured in microvolts (μ V). MEP latencies were measured as the time in milliseconds (ms) from the point at which a TMS pulse was delivered to the onset of a MEP. MEP amplitude and latency analysis were performed on a desktop computer (DELL, Berkshire UK) using the program Signal (Version 4.0; Cambridge Electronic Design Ltd, Cambridge, UK). The mean of each set of 10 PMEP and APB MEP amplitudes and latencies (at baseline, 0 mins and 30 mins), were obtained before being converted to percentage changes from baseline.

Results

Patient recruitment commenced in 2019 and was stopped in 2020 during the COVID-19 pandemic due to the mandated cessation of research particularly, as in this case, research that has the potential to be aerosol-generating.

Twelve people with PD (pwPD) were consented and took part in the study (10 males and 2 females with a mean age of 70 (\pm 8) years) [Table 1](#). Five patients were randomly allocated to the 5 Hz rTMS group (4 male 1 female), 3 to the PES group (3 males) and 4 to the 1 Hz rTMS group (3 males 1 female). Mean ages in the 1 Hz rTMS, 5 Hz rTMS and PES groups were 71 (\pm 8), 67 (\pm 3) and 75 (\pm 12). All neuro-stimulatory procedures were well tolerated, implying clinical feasibility with no adverse effects occurring or being reported by study participants.

The mean Hoehn and Yahr scores in the 1 Hz, 5 Hz rTMS and PES rTMS groups were 2.9 (\pm 0.3), 2.1 (\pm 0.6) and 1.8 (\pm 0.3), respectively. The mean Schwab and England ADL score in the 1 Hz, 5 Hz rTMS and PES groups were 68% (\pm 13), 80% (\pm 12) and 87% (\pm 6).

Table 1. Demographic data for study participants.

Participants	Intervention	Sex	Age	Time since PD diagnosis	Hohen and Yarr	Schwab and England
1	1Hz	M	78	4	2.5	0.7
2	5Hz	M	63	3	2	0.8
3	5Hz	F	70	3	1.5	0.8
4	PES	M	62	5	1.5	0.8
5	1Hz	M	60	8	3	0.8
6	1Hz	M	70	5	3	0.7
7	1Hz	F	76	6	3	0.5
8	5Hz	M	66	2	2	0.9
9	PES	M	83	3	2	0.9
10	5Hz	M	67	7	2	0.9
11	PES	M	81	6	2	0.9
12	5Hz	M	69	5	3	0.6

Cortical parameters

Seven participants had a dominant right-hemispheric pharyngeal motor area and 5 had a dominant left hemisphere. These remained stable across studies.

The mean pharyngeal RMT over the dominant hemisphere was 77% ($\pm 9\%$) and 69% ($\pm 11\%$) over the non-dominant hemisphere. The mean APB RMT was 43% ($\pm 13\%$).

Using the cranial vertex as a reference point from which to calculate x and y co-ordinates, mean cortical pharyngeal motor areas were located at $x = 3.9$ cm (± 1.1 cm) and $y = 2.6$ cm (± 1.7 cm) over the right hemisphere and $x = -2.5$ cm (± 3.6 cm) and $y = 2.5$ cm (± 1.7 cm) over the left hemisphere. APB motor areas were located at $x = 4.7$ (± 0.5 cm) and $y = 1.3$ (± 0.9 cm) over the right hemisphere and $x = -4.8$ cm (± 1.4 cm) and $y = 1.9$ cm (± 2.1 cm) over the left hemisphere.

Penetration aspiration scores

Mean and median cPAS for each group can be seen in [Table 2](#).

Thin fluids. Mean percentage differences from baseline PAS for thin fluids in the 1 Hz rTMS, 5 Hz rTMS and PES groups were 2.09 (SD: 35.00), 0.49 (SD: 24.50) and -10.53 (SD: 18.23) in the active arms compared with 53.57 (SD: 87.77), 18.97 (SD: 57.83) and 103.25 (SD: 171.36) respectively in the sham arms ([Figure 2](#)).

Paste. In the active arms mean percentage differences from baseline for the 1 Hz and PES groups were -16.67 (SD: 23.57) and -19.05 (SD: 32.99) compared with -5 (SD: 0) and 55.56 (SD: 69.39) in the sham arms ([Figure 3 A+B](#)). The 5 Hz

rTMS group could not be analysed as all swallows with paste consistency were <2 (hence normal) for both active and sham arms for all time points.

Solid. In the PES group, the mean percentage difference from baseline was -20.0 (SD: 34.64) in the active arm and 122.22 (SD: 107.15) in the sham arm ([Figure 3 C](#)). Solid swallows in the 5 Hz and 1 Hz rTMS groups resulted in PAS values of <2 (hence normal) in both active and sham arms. As such no analysis could be performed.

Cup drinking (IDDSI 0). With regards to cup drinking, mean percentage difference in means from baseline in the active 1 Hz rTMS, 5 Hz rTMS and PES groups were 0 (SD: 0), -32.29 (SD: 28.94) and -12.5 (SD: 17.68) respectively compared to -24.44 (SD: 21.43), -4.17 (SD: 54.65) and 0 (SD: 47.14) respectively in the sham arms ([Figure 3 D+E](#)).

Swallow timing results

Raw timing data for thin fluids can be seen in [Table 3](#).

Oral transit time. Mean percentage changes in OTT from baseline in the active 1 Hz rTMS, 5 Hz rTMS and PES groups were 16.0 (SD: 42.46), 3.38 (SD: 16.75) and 0.01 (SD: 57.02) and -20.26 (SD: 28.62), 9.02 (SD: 26.70) and 3.71 (SD: 64.56) respectively.

Pharyngeal response time. Percentage changes from baseline in the 1 Hz rTMS, 5 Hz rTMS and PES groups were -24.78 (SD: 40.80), 9.29 (SD: 22.26) and -2.83 (SD: 19.58) in the active arms respectively. In the sham arms values were 38.0 (SD: 59.91), 17.44 (SD: 21.84) and 21.86 (SD: 28.46) respectively.

Table 2. cPAs data for each interventional group.

			Mean		Median	
			Pre	Post	Pre	Post
1 HZ	Active	Thin	18.8 ± 5.9	18.0 ± 2.1	21.5	15.0
		Paste	4.5 ± 1.7	3.5 ± 0.0	4.5	3.5
		Solid	3.0 ± 0.0	3.0 ± 0.0	3.0	3.0
		Cup drinking	5.0 ± 3.5	3.0 ± 0.0	4.0	3.0
	Sham	Thin	14.0 ± 8.4	16.0 ± 1.1	15.5	14.5
		Paste	3.8 ± 1.0	3.5 ± 0.4	3.5	3.0
		Solid	3.3 ± 0.5	3.3 ± 0.2	3.0	3.0
		Cup drinking	6.0 ± 3.7	3.0 ± 0.0	5.5	3.0
5 HZ	Active	Thin	12.3 ± 3.3	13.0 ± 5.6	11.0	11.0
		Paste	3.0 ± 0.0	3.0 ± 0.0	3.0	3.0
		Solid	3.0 ± 0.0	3.0 ± 0.0	3.0	3.0
		Cup drinking	6.8 ± 3.0	3.6 ± 1.3	7.0	3.0
	Sham	Thin	12.8 ± 4.7	13.6 ± 6.1	11.0	10.0
		Paste	3.0 ± 0.0	3.0 ± 0.0	3.0	3.0
		Solid	3.0 ± 0.0	3.0 ± 0.0	3.0	3.0
		Cup drinking	4.6 ± 1.9	4.3 ± 2.2	4.0	4.0
PES	Active	Thin	12.3 ± 5.9	10.3 ± 2.5	10.0	10.0
		Paste	6.7 ± 6.4	4.0 ± 1.7	3.0	3.0
		Solid	5.3 ± 4.0	3.3 ± 0.6	3.0	3.0
		Cup drinking	4.0 ± 0.0	3.5 ± 0.7	4.0	3.5
	Sham	Thin	10.0 ± 7.0	12.3 ± 4.0	13.0	13.0
		Paste	3.0 ± 0.0	4.7 ± 2.1	3.0	4.0
		Solid	3.0 ± 0.0	6.7 ± 3.2	3.0	8.0
		Cup drinking	4.5 ± 2.1	5.0 ± 4.2	4.5	5.0

Pharyngeal transit time. Mean PTT percentage changes from baseline in the active arms of the 1 Hz rTMS, 5 Hz rTMS and PES groups were 11.83 (SD: 8.53), 0.66 (SD: 29.79) and 36.72 (SD: 83.61) respectively and 4.53 (SD: 16.52), 24.25 (SD: 35.63) and 30.64 (SD: 34.10) in the sham arms respectively (Figure 4 B).

Motor evoked potentials

Median values for baseline MEP amplitudes and latencies can be seen in Table 4. Comparing mean percentage changes in amplitudes between ‘dominant’ and ‘non-dominant’ pharyngeal motor hemispheres did not reveal a significant difference for 1 Hz rTMS, 5 Hz rTMS or PES (Paired T-Test: $T_5 = 0.99$, $P = 0.37$, $T_9 = 0.75$, $P = 0.47$ and $T_5 = 1.76$, $P = 0.14$). Hence data

were merged to produce a combined hemispheric value as previously reported^{24,28}.

Amplitudes

Pharyngeal

Mean percentage change from baseline PMEP amplitudes in the active arm of the 1 Hz rTMS group were -2.01 (SD: 34.58) at 0 minutes and 31.55 (SD: 85.11) at 30 minutes compared to sham values of 17.30 (SD: 31.55) and 24.34 (SD: 40.70) (Figure 5 A+C). In the 5 Hz rTMS group values in the active arm were 14.98 (SD: 28.43) at 0 minutes and 3.52 (SD: 37.95) at 30 minutes compared to -3.83 (SD: 26.99) and -16.09 (SD: 36.36) in the sham arm. In the active arm of the PES group, values at 0 and 30 minutes were 9.73 (SD: 36.58) and

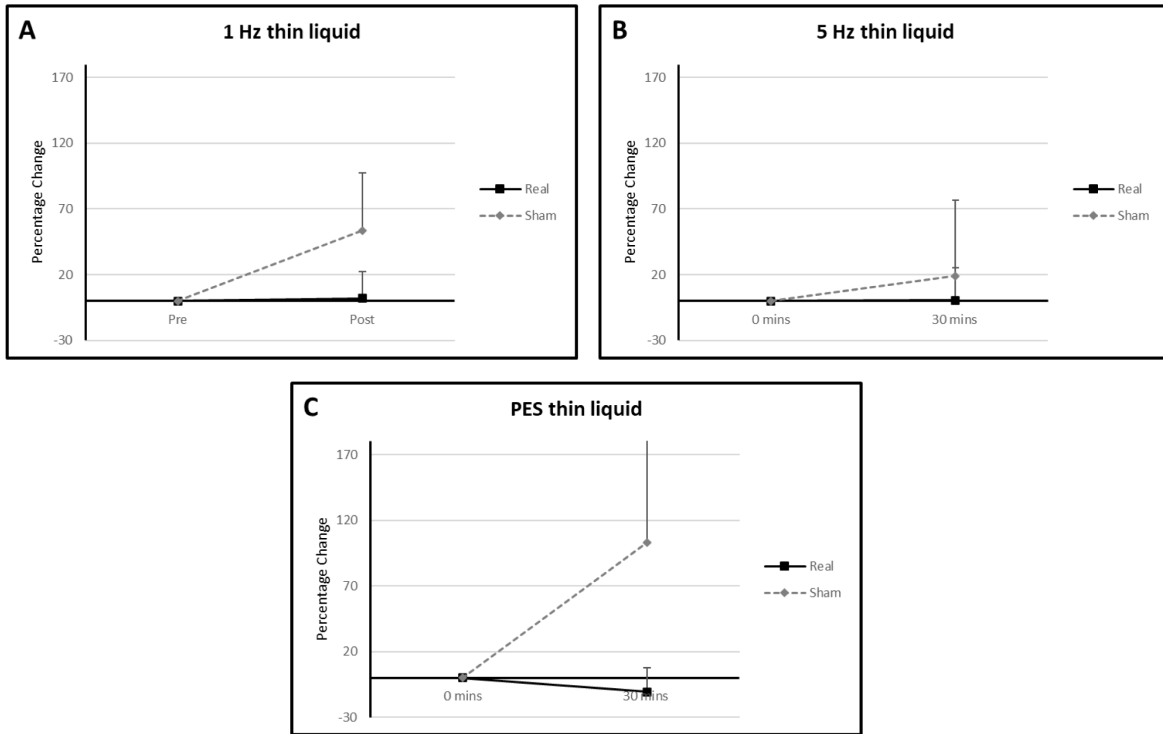


Figure 2. Graphs of percentage differences in PAS for thin fluid in the (A) 1 Hz rTMS, (B) 5Hz rTMS and (C) PES interventional groups. Error bars illustrate standard deviations at each data point.

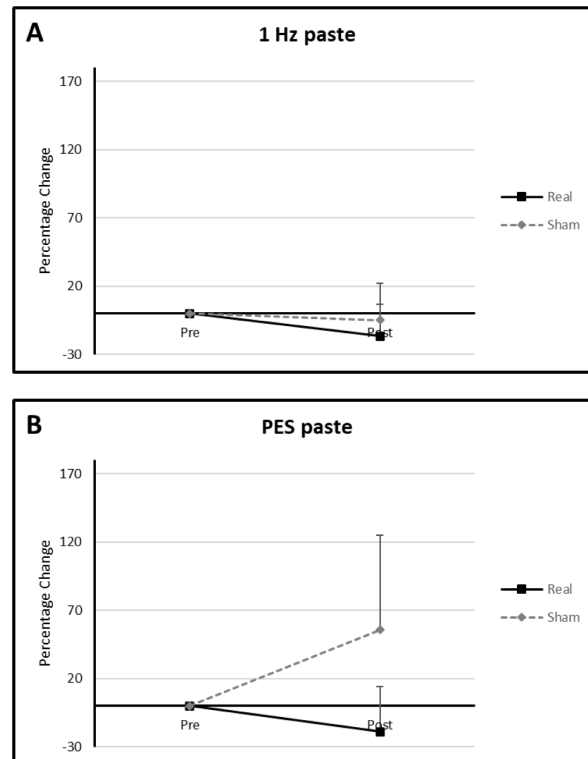


Figure 3. Graphs of percentage differences in PAS for paste consistency in the (A) 1 Hz rTMS and (B) PES interventional groups.

Table 3. Swallowing timing data.

		Active			
		Mean (ms)		Median (ms)	
		Pre	Post	Pre	Post
1 Hz	OTT	362 ± 193	470 ± 416	301	250
	PRT	681 ± 646	395 ± 274	423	250
	PTT	447 ± 168	501 ± 198	372	392
5 Hz	OTT	344 ± 133	343 ± 193	365	380
	PRT	180 ± 325	216 ± 212	193	234
	PTT	411 ± 117	387 ± 51	456	407
PES	OTT	298 ± 73	310 ± 188	276	417
	PRT	547 ± 443	496 ± 334	303	362
	PTT	464 ± 192	578 ± 257	360	570
		Sham			
		Mean (ms)		Median (ms)	
		Pre	Post	Pre	Post
1 Hz	OTT	470 ± 241	344 ± 121	396	310
	PRT	519 ± 512	922 ± 1182	298	335
	PTT	510 ± 161	548 ± 256	421	434
5 Hz	OTT	374 ± 82	419 ± 183	372	395
	PRT	268 ± 160	307 ± 161	198	288
	PTT	351 ± 83	414 ± 38	310	400
PES	OTT	419 ± 128	389 ± 196	360	350
	PRT	480 ± 252	560 ± 219	389	598
	PTT	326 ± 80	439 ± 215	288	360

15.01 (SD: 35.34) compared to 3.93 (SD: 31.92) and -6.63 (SD: 41.17) in the sham arm.

APB

Mean percentage changes from baseline for APB MEP amplitudes in the active arm of the 1 Hz rTMS group were -26.49 (SD: 61.25) at 0 minutes and -43.77 (SD: 53.02) at 30 minutes compared to sham values of 35.58 (SD: 33.97) and 32.30 (SD: 35.78) (Figure 5 B+D). In the active arm of the 5 Hz rTMS interventional group percentage changes from baseline were -13.56 (SD: 60.01) at 0 minutes and 25.68 (SD: 57.79) at 30 minutes contrasted with 3.16 (SD: 69.86) and 18.32 (SD: 83.34) in the sham arm. In the PES group, values at 0 and 30 minutes in the active arm were -35.98 (SD: 50.94)

at 0 minutes and -49.73 (SD: 68.54) at 30 minutes compared to -13.90 (SD: 61.10) and 71.55 (SD: 82.23).

Latencies

Pharyngeal

Mean percentage change from baseline PMEP latencies in the active arm of the 1 Hz rTMS group at 0 and 30 minutes were -6.99 (SD: 9.89) and -2.20 (SD: 6.38) compared to sham values of 5.88 (SD: 5.17) and -3.73 (SD: 4.80) (Figure 5 A+C). In the 5 Hz rTMS group, values in the active arm at 0 and 30 minutes were 3.35 (SD: 9.23) and 4.53 (SD: 9.35) compared to -2.73 (SD: 9.13) and 1.07 (SD: 8.60) in the sham arm. In the active arm of the PES group, values at 0 and 30 minutes were 1.49 (SD: 4.05) and -3.41 (SD: 4.88) compared to -0.42 (SD: 4.69) and -2.57 (SD: 1.07) in the sham arm.

APB

Mean percentage changes from baseline for APB MEP latencies in the active arm of the 1 Hz rTMS group were -1.63 (SD: 5.62) at 0 minutes and 0.82 (SD: 5.64) at 30 minutes compared to sham values of -1.61 (SD: 2.45) and -5.54 (SD: 5.00) (Figure 5 B+D). In the active arm of the 5 Hz rTMS interventional group percentage changes from baseline were 1.97 (SD: 9.44) at 0 minutes and -2.48 (SD: 4.45) at 30 minutes compared to 5.31 (SD: 7.98) and 1.05 (SD: 4.51) in the sham arm. In the PES group, values at 0 and 30 minutes in the active arm were -1.99 (SD: 7.60) at 0 minutes and 1.87 (SD: 4.18) at 30 minutes compared to -8.75 (SD: 11.02) and 9.09 (SD: 8.90).

Discussion

Despite the small size of the study, our findings merit further discussion.

PAS

Interestingly, across all interventions there was a clear graphical separation between active and sham results, with active stimulation consistently having a lower PAS, and hence appearing to be more physiological beneficial, than sham. A potential reason why sham stimulation resulted in higher PAS scores than active stimulation is due to patient fatigue during the course of a study session. It may be that, were more patient data available, statistical analysis and clarity on efficacy may have been possible for one or more interventions. Our findings share some similarities with the results of the only rTMS study performed in PD related dysphagia. In 2019 Khedr *et al* studied 33 patients with PD and found the application of 20 Hz rTMS to the hand motor cortex led to improvements in pharyngeal transit time for thin fluids and solids³⁰. However, no significant differences were seen regarding PAS values.

More broadly, a meta-analysis conducted in 2015 by Chou *et al* demonstrated that high-frequency rTMS led to improvements in PD related limb motor dysfunction⁴⁰. However, it should be recognised that the picture regarding the use of high-frequency rTMS to treat PD motor symptoms is a relatively mixed one with another meta-analysis by Shukla *et al* not showing

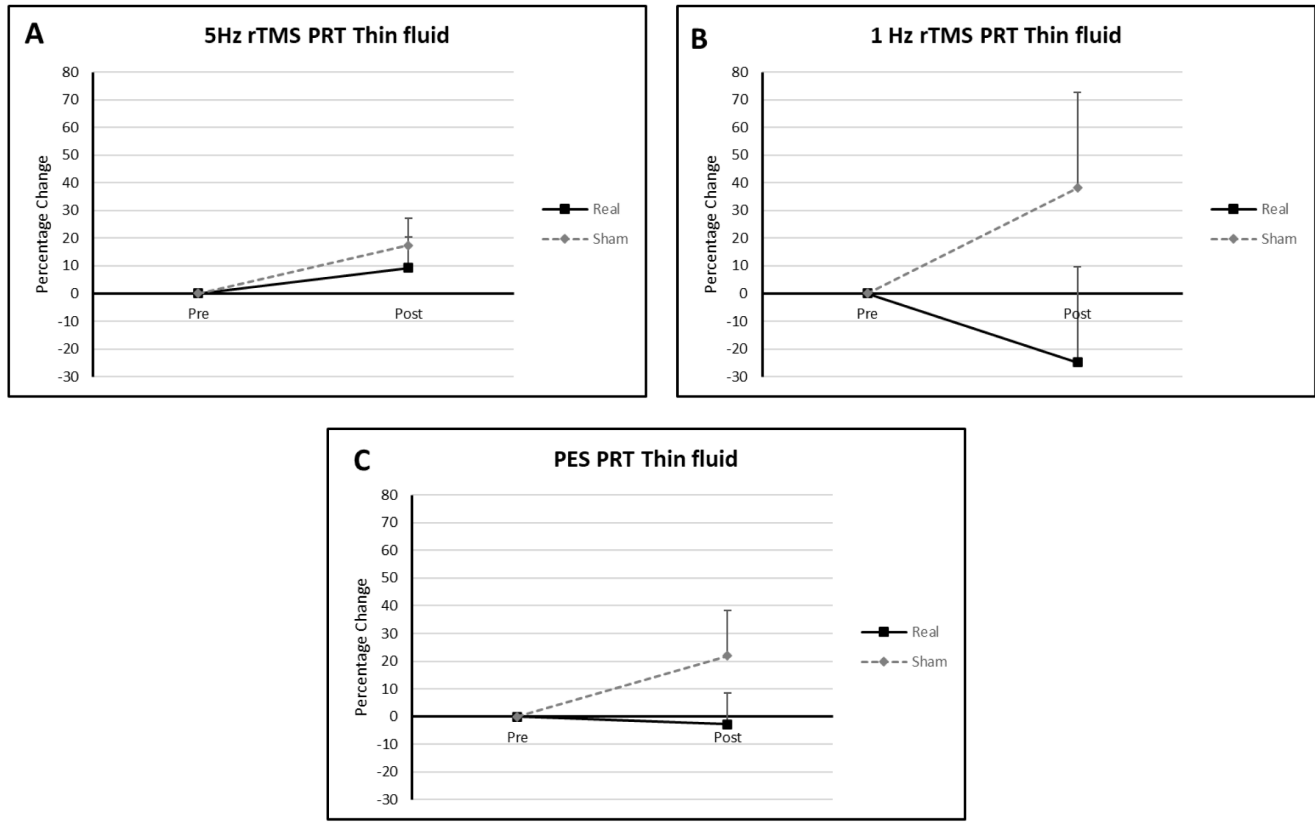


Figure 4. Graphs of percentage differences in PRT in the 1 Hz rTMS, 5 Hz rTMS and PES groups (A, B, C).

Table 4. Median (+/- interquartile range) cortical pharyngeal and cortical APB MEP amplitudes in microvolts (μ V) and latencies in milliseconds (ms) .

	5 Hz rTMS		PES		1 Hz rTMS	
	Baseline	30mins	Baseline	30mins	Baseline	30mins
MEP amplitudes (μV)						
Cortical pharyngeal	90.9 \pm 27.4	103.1 \pm 7.7	62.2 \pm 23.7	67.1 \pm 19.3	253.5 \pm 71.7	169.6 \pm 63.6
Cortical APB	47.8 \pm 66.0	41.3 \pm 114.9	573.8 \pm 10.8	252.6 \pm 92.2	2431.5 \pm 1260.5	251.6 \pm 548.0
MEP latencies (ms)						
Cortical pharyngeal	7.9 \pm 1.1	8.6 \pm 0.7	8.9 \pm 0.3	8.6 \pm 0.2	9.7 \pm 0.5	10.1 \pm 0.6
Cortical APB	25.3 \pm 2.1	24.4 \pm 1.5	23.1 \pm 1.1	23.2 \pm 1.0	23.7 \pm 0.4	24.4 \pm 0.7

a clear benefit²⁶. In the literature, while there are no studies applying 1 Hz rTMS to PD dysphagia, a meta-analysis of the effects of 1 Hz rTMS on motor symptoms in PD showed a significant post interventional improvement²⁶. However, similar to the mixed picture for high-frequency rTMS, a recent meta-analysis did not show that 1Hz rTMS can induce motor improvement⁴⁰, therefore, no firm conclusions can be made.

Swallowing timing

The visual improvements in PRT observed for thin fluids particularly in the 1 Hz rTMS and PES groups are comparable to the improvement in PTT for solids observed by Khedr *et al.* in 2019³⁰. These results, imply that both excitatory (PES in this study and 20 Hz rTMS in the Khedr study) and inhibitory (1Hz rTMS) neurostimulation have the potential to affect

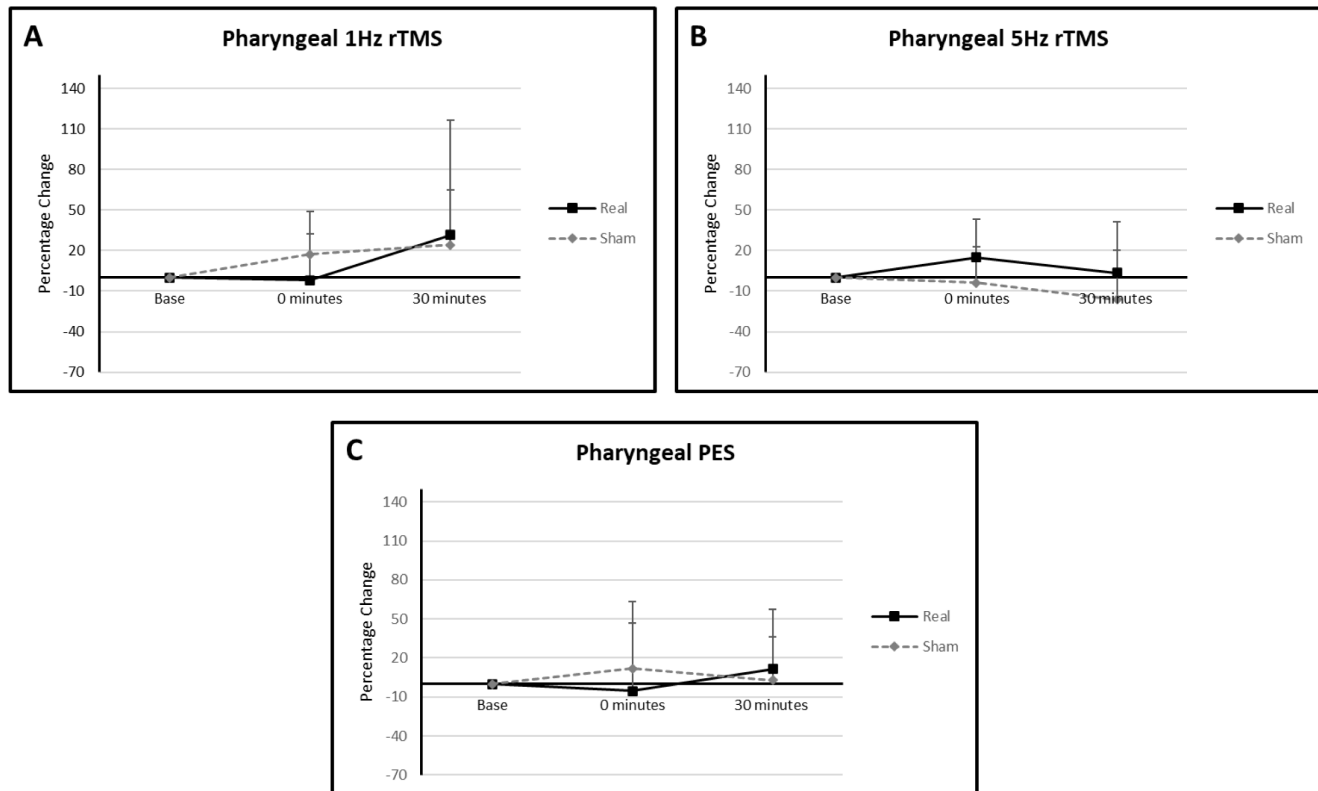


Figure 5. Graphs of percentage differences in PMEP amplitudes in the 1 Hz rTMS (A), (B) 5Hz rTMS and (C) PES interventional groups. Error bars illustrate standard deviations at each data point.

swallowing physiology and by so doing improve swallowing function.

MEP

With regards PMEP amplitudes, despite the small number of participants in each interventional group, some minor separation of the trend lines began to emerge between sham and active stimulation for 1 Hz rTMS, 5 Hz rTMS and PES. In more detail, in the 5 Hz rTMS and PES interventional groups, interventions which have been shown to provoke cortical excitation within the swallowing motor system^{24,39}, there was the suggestion of greater PMEP amplitudes in the active treatment arms compared to sham. This was also the case following 1 Hz rTMS which is known to cause cortical suppression⁴¹. Were the groups larger, some significance may have eventually emerged. Despite no previous PD studies having been performed wherein rTMS was delivered to pharyngeal motor cortical swallowing areas (the 2019 Khedr study only stimulated the hand motor area³⁰), these findings are tentatively supportive of the multiple studies which show high-frequency rTMS leads to increased PMEP amplitudes^{21,24,28}. With regards to 1 Hz rTMS which has been shown to be suppressive when applied over the pharyngeal motor cortex³⁵, there was some suggestion that the sham group had greater PMEP amplitudes than the active group. However small numbers make drawing any conclusions from this, premature.

PD symptom and ADL scores

We did note that the H&Y score was higher in the 1Hz rTMS interventional group than the other intervention arms. Despite participants being allocated at random, this indicates participants in the 1 Hz rTMS group had slightly more severe PD symptoms than those in the other groups. By contrast, there were no differences in Schwab and England ADL scores across any of the intervention arms. The significance of the Hoehn and Yahr differences is unclear given similar ADL performances between groups which implies that participants in the 1Hz rTMS group were still as fit and able as participants in the other interventional groups.

Limitations

Our study has several limitations. First, the number of patients that were able to be recruited was small. Patient recruitment was negatively impacted by several issues many of which were logistical and not in the control of the research team. Some examples include: there was some anecdotal evidence that emerged during the study which suggested patients with moderate PD were not as troubled by their relatively mild dysphagia as they were by their limb motor symptoms. This may explain why relatively few patients reached out to the research team regarding study participation. Conversely, patients with severe dysphagia were often too frail to be studied in a laboratory setting.

Another limitation was the onset of COVID-19 pandemic and research restrictions that were put in place to prevent the spread of the virus. Swallowing research, especially research involving pharyngeal intubation, is potentially aerosol generating meaning patient recruitment was stopped more than 6 months prior to the planned end date. This reduction in recruitment lead to reduced power and hence contributed to difficulty in drawing definitive conclusions from the study

MEP recordings were only made up to 30 minutes post-stimulation. This was done to reduce the time patients had to be present in the laboratory thereby making the experience more tolerable and reducing dropout. However, most healthy participant neurophysiological studies which measure MEP amplitudes record for up to an hour post stimulation^{24,42}. Furthermore, in these studies, maximal separation between interventional groups tends to occur at times between 30 and 60 minutes^{37,42}. Therefore, in only making recordings up to 30 minutes post intervention, any delayed effects of neurostimulation might be missed.

Lastly, PAS was used to assess swallowing function within our study. However, while it remains a commonly used and validated method of swallowing assessment, in clinical practice and in research, it is not a perfect assessment of swallowing function³³. One of its limitations is its inability to quantify the amount of each bolus that is aspirated³³.

Conclusion

In conclusion, the use of neurostimulation in patients with PD dysphagia is well tolerated and might lead to some improvements in swallowing function, however suboptimal

recruitment precludes more definitive conclusions. Larger studies will be needed to further answer the important question of does neuromodulation improve swallowing in PD associated dysphagia, in this understudied area of medicine.

Data availability

Figshare. Parkinsons study data AOS.xlsx. DOI: <https://doi.org/10.48420/14958540.v1>⁴³

This project contains the following data:

- Data from a feasibility pilot study of the effects of neurostimulation on dysphagia recovery in Parkinson's Disease

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC BY 4.0 Public domain dedication).

Figshare. Study Protocol: Exploring Novel Neurostimulation Based Therapies for Swallowing Impairments in Parkinson's Disease. DOI: <https://doi.org/10.48420/14995077.v1>⁴⁴

Figshare. CONSORT checklist for study "A feasibility pilot randomised controlled study of the effects of neurostimulation on dysphagia recovery in Parkinson's Disease" DOI: <https://doi.org/10.48420/15082662.v1>⁴⁵

Figshare. CONSORT flowchart for the study "A feasibility pilot randomised controlled study of the effects of neurostimulation on dysphagia recovery in Parkinson's Disease". DOI: <https://doi.org/10.48420/15082674.v2>⁴⁶

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Reviewer Report 25 April 2022

<https://doi.org/10.21956/amrcopenres.14146.r26966>

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Paul Muhle 

Department of Neurology with Institute of Translational Neurology, University Hospital Muenster, Muenster, Germany

Thank you for giving me the opportunity to review this manuscript. This is an interesting feasibility study on the effects of 1 Hz rTMS, 5 Hz rTMS and PES in dysphagic PD patients. The topic certainly is relevant since dysphagia occurs frequently in this group of patients and not only leads to an increased risk of aspiration/penetration and its sequelae but can also cause an impaired quality of life and increases the risk for malnutrition and exsiccosis. Therapeutic options are limited which make approaches like the one presented in this study welcome and necessary. Even more so if different neurostimulation techniques and stimulation parameters are compared to identify the most effective treatment. The study and manuscript are well-structured, and the language is sound. It is a pity that COVID would not allow for a better recruitment which in my opinion is the major limitation of this study. This is stressed in the manuscript and - as already pointed out - not the researchers fault considering the pandemic related constraints to studies worldwide. There are only few minor comments that I would like to add for possible improvement of the manuscript:

- For an even more precise characterization of the participants and to allow for a better comparison to PD collectives in other investigations, would it be possible to provide data on the UPDRS part III and Levodopa-equivalent dose? Hoehn & Yahr is a relatively "rough" characterization of disease severity in these patients. Also, if possible, the motor subtype may be added. We know that for example tremor-dominant types respond to DBS particularly well regarding their motor symptoms. Considering rTMS and PES it may be of interest (of course later and larger studies) to include specification of the subtype and evaluate possible different responses to these treatments.
- The limitation of using PAS in research is already described in the limitations section of the manuscript. However, I believe that it may be worth another one or two sentences to describe the limitations more closely and for example explain that a major pathologic finding in PD-related dysphagia are residues which are not part of the PAS. Hence, a possible aim of improved swallowing efficiency by reducing residue by treatment – analog

to recent findings in EMST – cannot be identified.

All in all, despite the limitations mentioned above, I believe this is an interesting manuscript worth being published in AMRC Open Research serving as model for a larger study once the main obstacles that COVID has caused are cleared.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: neurogenic dysphagia

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 01 December 2021

<https://doi.org/10.21956/amrcopenres.14082.r26847>

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Corinne A. Jones

¹ Department of Neurology, Dell Medical School, The University of Texas at Austin, Austin, TX, USA

² Department of Speech, Language, and Hearing Sciences, Moody College of Communication, The University of Texas at Austin, Austin, TX, USA

This study investigated the feasibility of one session of 1Hz rTMS, 5Hz rTMS, and PES to impact swallowing physiology in individuals with PD and dysphagia. Given the low number of patients recruited, the authors did not assess statistical differences but instead looked at trends. Please find my comments below.

General

1. This is a small point, but there is no dysphagia recovery in PD, given the progressive neurodegeneration. Consider changing the title of the study.
2. Be consistent with use of abbreviations (e.g., PAS vs PAs or rTMS vs RTMS) and be sure that each abbreviation is defined (e.g., RMT is not defined)

Abstract

3. The phrase "there was visual separation in a positive direction" does not have much meaning and does not fully capture the results, particularly those where there were no changes for the active group but there was worsening of function for the sham group (e.g., Figure 2)

Introduction

4. A major missing piece is the rationale for using rTMS and PES for PD-associated dysphagia. The fact that there haven't been any studies yet is not a strong enough rationale. What about PD would cause rTMS or PES to be successful?

5. Please state your hypotheses

Methods

6. Please consider reorganizing the Methods section for easier reading (e.g., move the Protocol section to be sooner)

7. How was PD diagnosis confirmed?

8. How were symptoms of dysphagia identified?

9. What bolus was scored for the PAS in the screening VFS?

10. Define the PAS, OTT, PTT, and PRT for reproducibility and for those readers who may not be familiar

11. PAS is not a gold standard, and has several limitations. Please remove the "gold standard" phrasing and discuss weaknesses of the PAS in the Discussion

12. The Cumulative PAS is not a commonly-used metric, and is misleading in this study, as 10 thin liquid boluses were collected but only 3 paste and 3 solid swallows.

13. What was the solid that was swallowed?

14. Was the fluoroscopy pulsed or continuous?

15. Please perform reliability testing for all of the videofluoroscopic metrics

16. The authors mention a criterion for statistical significance, but do not mention any actual statistical test performed

17. Consider reporting raw change for the PAS values, as the PAS is an ordinal scale

18. Were the patients in the ON or OFF state of their PD medication?

19. The intervention is not clear in Figure 1. Please add more detail. Did each patient receive active and sham stimulation? If so, how long between sessions?

20. What was the criteria for 'visual improvement'?

Results

21. The percent change of PAS in Figure 2 does not match the mean or median change in Table 2. Please explain.

22. Please present the pre and post MEPs in Table 4

Discussion

23. The statement about tolerance belongs in the Results. Also, what was assessed specifically in regards to tolerance?

24. How can the worsening of function in the sham group (figures 2-4) be described?

25. There does not appear to be much change in the MEP, despite what the authors report.

26. Another large limitation that the authors do not address is the single session nature of the study. The previous neurostimulation papers that are referenced have a series of sessions of neurostimulation, which would be more ecologically valid

27. COVID-19 has negatively affected many swallowing projects, but it is not clear why recruitment was ended so early for this study

References

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Swallowing physiology; dysphagia rehabilitation; Parkinson's disease
dysphagia; noninvasive neurostimulation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Mar 2022

Ayodele Sasegbon, University of Manchester, Manchester, UK

Reviewer 2

General

1. This is a small point, but there is no dysphagia recovery in PD, given the progressive neurodegeneration. Consider changing the title of the study.

The title has been changed to "A feasibility pilot study of the effects of neurostimulation on swallowing function in Parkinson's Disease".

2. Be consistent with the use of abbreviations (e.g., PAS vs PAs or rTMS vs RTMS) and be sure that each abbreviation is defined (e.g., RMT is not defined)

Thank you for your input. Changes have been made to ensure consistency. Resting motor threshold (RMT) was defined on page 5 of the initial paper.

Abstract

3. The phrase "there was visual separation in a positive direction" does not have much meaning and does not fully capture the results, particularly those where there were no changes for the active group but there was worsening of function for the sham group (e.g., Figure 2)

A change has been made to the text so it now reads "there was small but visible difference in the outcomes between active and sham".

Introduction

4. A major missing piece is the rationale for using rTMS and PES for PD-associated dysphagia. The fact that there haven't been any studies yet is not a strong enough rationale. What about PD would cause rTMS or PES to be successful?

PD is a cause of neurogenic dysphagia. A means by which PD leads to dysphagia is

neuronal damage to cortical swallowing centres. This damage causes a measurable reduction in activity over cortical swallowing centres. While the disease and mechanism of damage are different in post-stroke dysphagia, its effects are also caused by damage to cortical swallowing centres. As rTMS and PES are two techniques which have been shown to be effective at improving swallowing function in post-stroke dysphagia by modulating the activity of cortical swallowing centres thereby encouraging beneficial neuroplastic changes, it was hypothesised that similar beneficial (compensatory) swallowing changes could be induced in patients with PD associated dysphagia. Furthermore, as stated in the introduction, rTMS has been used, to moderate effect, to treat PD motor symptoms affecting the limbs. In this context, both inhibitory 1 Hz and excitatory 5 Hz rTMS have been shown to be effective. As a result, it was not unreasonable to hypothesise that dysphagia may also be amenable to being ameliorated using neuromodulatory techniques such as rTMS and PES. This has been further clarified in the text.

5. Please state your hypotheses

This has been added to the text

Methods

6. Please consider reorganizing the Methods section for easier reading (e.g., move the Protocol section to be sooner)

The methods section has been reorganised

7. How was PD diagnosis confirmed?

Only patients with a documented diagnosis of PD from a Neurologist were recruited. Furthermore, the diagnosis had to have been made at least two years prior to the start of the study. This information was detailed on page 3 of the first version of the paper.

8. How were symptoms of dysphagia identified?

On page 3 of the first version of the paper, patients were initially recruited based on self-reported symptoms of dysphagia. These would later be confirmed or refuted based on their initial videofluoroscopy.

9. What bolus was scored for the PAS in the screening VFS?

On page six of the first version of the paper we explained that the PAS with the highest numerical value was recorded for each bolus (in the case of multiple swallows) before being added together for each category (thin fluid, paste, solid and cup drinking). This has been stated in other parts of the text for additional clarity.

10. Define the PAS, OTT, PTT, and PRT for reproducibility and for those readers who may not be familiar

These have been defined in the text for clarity.

11. PAS is not a gold standard, and has several limitations. Please remove the "gold standard" phrasing and discuss weaknesses of the PAS in the Discussion

References to PAS as a gold standard have been removed from the text. However, it is true to say that PAS is one of the most validated tools for the assessment of dysphagia in the field.

12. The Cumulative PAS is not a commonly-used metric, and is misleading in this study, as 10 thin liquid boluses were collected but only 3 paste and 3 solid swallows.

cPAS is a valid metric (6) that has been used in similar studies of this type (7) and was not selected to mislead. As long as the number of swallows is stated (10 thin liquid, 3 paste and 3 solid), as has been done in the text, we believe there should be no undue confusion.

13. What was the solid that was swallowed?

On page 4 of the initial version of the paper, the solid that was swallowed was stated to be a biscuit covered in barium sulphate.

14. Was the fluoroscopy pulsed or continuous?

VFS was continuous. This has been added to the text for clarity

15. Please perform reliability testing for all of the videofluoroscopic metrics

VFS recordings were anonymised and independently analysed by IC, a qualified speech and language therapist who was blinded to the data being analysed. The metrics used - PAS, OTT, PTT, and PRT - have been used and validated in previous studies in neurogenic dysphagia. The performance of reliability testing was out of scope for this small feasibility study, and given that all VFS were analysed by one individual, there was no concern that there would be intra-rater variation.

16. The authors mention a criterion for statistical significance, but do not mention any actual statistical test performed

Our original intention was to statistically analyse our data, but due to poor recruitment, it would have been inappropriate to subject the data we collected to statistical analysis due to the high risk of type II errors.

References to statistical analysis have been removed from the text for clarity.

17. Consider reporting raw change for the PAS values, as the PAS is an ordinal scale

The method of reporting percentage changes from individual baseline has been used in several papers published in the field (8, 9). We do not believe that the addition of another table or another layer of analyses looking at raw changes from individual baseline would provide any additional information with respect to the key study findings.

18. Were the patients in the ON or OFF state of their PD medication?

The patients were in the ON state at the time of being studied. This has been added to the text.

19. The intervention is not clear in Figure 1. Please add more detail. Did each patient receive active and sham stimulation? If so, how long between sessions?

Yes, patients received active and sham stimulation within their interventional groups.

At least a week separated each session. This information was on page 6 of the initial version of the paper.

20. What was the criteria for 'visual improvement'?

The term visual improvement was meant to indicate there was the appearance of change in favour of the treatment arm, but this was not quantifiable statistically.

Results

21. The percent change of PAS in Figure 2 does not match the mean or median change in Table 2. Please explain.

The values in table 2 are raw cPAS values while the values used in figure 2 are percentage changes from baseline.

22. Please present the pre and post MEPs in Table 4

An expanded table has been added to the text.

Discussion

23. The statement about tolerance belongs in the Results. Also, what was assessed specifically in regards to tolerance?

Tolerance was assessed by asking participants after each session how they felt and if had any post-intervention after-effects. This has been moved to the results section.

24. How can the worsening of function in the sham group (figures 2-4) be described?

A potential reason why sham stimulation resulted in higher PAS scores than active stimulation is due to patient fatigue during the course of a study session. This has been added to the discussion.

25. There does not appear to be much change in the MEP, despite what the authors report.

Thank you for this point. The MEP changes observed were minor and this has been stressed in the text. However, despite the study's limitations, at 30 minutes post intervention, amplitudes in the active groups were consistently raised compared to that observed in the sham groups.

26. Another large limitation that the authors do not address is the single-session nature of the study. The previous neurostimulation papers that are referenced have a series of sessions of neurostimulation, which would be more ecologically valid

This limitation has been added to the text. However, this study was designed to detect immediate post neurostimulation neurophysiological and swallowing behavioural changes.

27. COVID-19 has negatively affected many swallowing projects, but it is not clear why recruitment was ended so early for this study

Swallowing related studies at the University of Manchester were suspended during the pandemic due to concerns about the potential generation of aerosols during experimentation. This coincided with the PhD student, who was helping conduct the study, completing his PhD and returning to full time clinical practice. As a result, recruitment was ended, as there was no further funding to support the study post the

reopening of research at the University. The authors did not think it was necessary to add this amount of detail to the paper.

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Competing Interests: As previously stated

Reviewer Report 08 September 2021

<https://doi.org/10.21956/amrcopenres.14082.r26775>

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 Jin Woo Park 

Department of Physical Medicine and Rehabilitation, Dongguk University Ilsan Hospital, Gyeonggi-do, South Korea

The design and protocol of this study are very well structured. This study aimed to investigate the effect of three modes of non-invasive neurostimulation on dysphagia in patients with Parkinson's disease and these types of studies have already been conducted on stroke patients. However, due to the lack of participants, it has a fatal drawback as a study that cannot be concluded using only simple descriptions without undergoing statistical verification. As this reviewer gave up research due to COVID-19, I fully understand the feelings of the researchers, but the value of a paper with a simple explanation is bound to decrease. An additional disappointment is that although it was based on previous studies that noninvasive neurostimulation had an effect on other motor functions, there seems to be a lack of detailed explanation of what mechanism can change the swallowing function. Parkinson's disease is distinctly different from stroke, and the explanation of its mechanism must also be different.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neurorehabilitation especially dysphagia rehabilitation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 30 Mar 2022

Ayodele Sasegbon, University of Manchester, Manchester, UK

Reviewer 1

The design and protocol of this study are very well structured. This study aimed to

investigate the effect of three modes of non-invasive neurostimulation on dysphagia in patients with Parkinson's disease and these types of studies have already been conducted on stroke patients. However, due to the lack of participants, it has a fatal drawback as a study that cannot be concluded using only simple descriptions without undergoing statistical verification. As this reviewer gave up research due to COVID-19, I fully understand the feelings of the researchers, but the value of a paper with a simple explanation is bound to decrease. An additional disappointment is that although it was based on previous studies that noninvasive neurostimulation had an effect on other motor functions, there seems to be a lack of detailed explanation of what mechanism can change the swallowing function. Parkinson's disease is distinctly different from stroke, and the explanation of its mechanism must also be different.

Thank you for your points. Unfortunately due to inadequate patient recruitment no definitive conclusions with regard to rTMS and PES effectiveness in Parkinsons Disease (PD) could be drawn. It would also be unreasonable to apply any formal statistics to these data, due to the small numbers of patients in each group, meaning that type II errors would be very likely. However, we still believe the study has benefit in demonstrating that these techniques can be applied safely in patients with PD. With regards to the mechanism through which non invasive neurostimulation can improve swallowing in patients with PD, the following has been added to the text:

"In PD the nature of Lewy body deposition, neuronal damage and attempted neuroplastic compensation results in cortical areas with both decreased (1) and increased activity (2). Within the areas with decreased activity, damage can be said to have exceeded compensatory efforts while in areas with increased activity attempted compensation is ongoing but with unclear effectiveness. Cortical rTMS and PES have been hypothesised to encourage beneficial neuroplastic changes in the brains of patients with neurogenic dysphagia in two distinct ways. Firstly, high frequency (excitatory rTMS) or PES are excitatory and increase neuronal activity over cortical swallowing centres (3). This increase in activity can either reverse suppressed neuronal activity due to pathological damage, thereby restoring a more normal state of activity (4), or perhaps increase activity in non suppressed areas thereby acting as the trigger to encourage compensation for contralateral damage or restoration of normal activity in areas with disordered neuronal firing. Secondly, low frequency (suppressive rTMS) is thought to block maladaptive neuronal activity in the motor cortex thereby allowing beneficial neuroplastic changes to occur (5)." The latter may be helpful in PD where there may be excessive (dysfunctional) excitation, leading to behavioural improvements.

Competing Interests: As previously stated