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**Study Protocol**

**Full title:** Exploring Novel Neurostimulation Based Therapies for Swallowing Impairments in Parkinson's Disease

**Short title:** Dysphagia in Parkinson's patients: a neurostimulation study.

**Key features:**

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# **Introduction**

## **1.2. The clinical problem**

Parkinson's Disease (PD) has a prevalence of 1 in every 500 in the UK. A recent meta- analysis [[1](#_ENREF_1)] showed that at least a third of people diagnosed with PD (PwPD) experience dysphagia, the latter causing severe complications, worsening their quality-of-life, increasing the risks of further complications and sometimes may lead to death [[1-4](#_ENREF_1)].

## **1.3. Consequences of swallowing difficulties in PD**

These complications may include: a) malnutrition and/or dehydration caused by a decrease in the safety of swallowing and weight loss; and b) choking and tracheobronchial aspiration caused by unsafe swallowing. Unsafe swallowing may increase the incidence of respiratory infections and aspiration pneumonia; thus, increasing the mortality rate [[2](#_ENREF_2)]. Further, administration of medication can become a critical issue in people with swallowing disorders. Swallowing deficits often emerge in the early stages of PD and can become significantly debilitating in later stages of the disease [[3](#_ENREF_3)]. Even subtle changes in swallowing function can have a large psychosocial impact on the patient and the caregiver [[5](#_ENREF_5)].

# **Background and Literature Review**

In the UK, evidence shows that PwPD are highly dissatisfied with the current limited therapeutic approaches employed by the speech and language therapists (SLTs). These approaches are attempted by the PwPD with low compliance [[5](#_ENREF_5)]. The limited evidence base has been highlighted by systematic [[6](#_ENREF_6), [7](#_ENREF_7)] and Cochrane [[8](#_ENREF_8)] reviews. UK SLTs advise PwPD to use compensatory strategies, such as consistency/texture modification, change in posture and swallowing exercises [[5](#_ENREF_5)]. Such strategies may address the issue only temporarily, while the clinical effectiveness is still controversial. Noteworthy is the recent increase in studies utilising neurostimulation for PD motor symptoms [[9](#_ENREF_9)]. Repetitive transcranial magnetic stimulation (TMS) in particular has been increasingly used and has been reported as well-tolerated by PwPD [[10](#_ENREF_10)]. One particular paradigm, inhibitory (1Hz) repetitive TMS (rTMS), has been used in the recent literature with promising results. This brain stimulation paradigm delivered over 10 minutes is shown to modify the inhibitory and excitatory neurochemical processes in the area of interest [[11](#_ENREF_11), [12](#_ENREF_12)].

In our previous study, we have observed that PwPD may experience swallowing disorders both *on* and *off* medication, or only *on* medication and some may not experience any swallowing disorders. For people with swallowing disorders both *on* and *off* medication, we observed an increase in excitation in the brain that represent and control the swallowing musculature [[2](#_ENREF_2)]. Building on these findings [[2](#_ENREF_2)], our contention is that manipulation of increased cortical excitability observed in PwPD with dysphagia while on dopaminergic medication could provide a therapeutic avenue for dysphagia.

The motor cortex hyperactivity seen in our studies is suggested to be attributed to a compensatory cortical reorganisation secondary to medication-induced re-afferentation of the deficient subcortical motor system. Given that there is enough data to show that dopaminergic medication may induce changes in cortical interactions and plasticity [[13](#_ENREF_13), [14](#_ENREF_14)], we are interested to see how we can modulate the cortical reorganisation in dysphagic PwPD with neurostimulation techniques.

Here, at the University of Manchester, we have pioneered a number of neurostimulation paradigms for swallowing rehabilitation in neurogenic dysphagia. The rTMS paradigms have been developed to enhance or suppress swallowing cortical representation [[15](#_ENREF_15), [16](#_ENREF_16)] and have shown changes in behaviour and cortico-pharyngeal pathway excitability (inhibitory 1 Hz [[15](#_ENREF_15)], excitatory 5 Hz rTMS [[16](#_ENREF_16), [17](#_ENREF_17)]). In addition, electrical stimulation applied peripherally to pharyngeal musculature has shown to promote swallowing rehabilitation in acute and chronic dysphagic patients with stroke lesions [[18-21](#_ENREF_18)].

# **Hypothesis**

Our primary hypothesis is that neurostimulation approaches in dysphagic PwPD will induce short-term changes in swallowing neurophysiology, with concurrent beneficial changes in swallowing efficiency and safety, as assessed by trigeminal and cortical pharyngeal pathways excitability and formal swallowing examinations with imaging.

# **Aims**

We aim to investigate, the effects of 3 different neurorehabilitation techniques for dysphagia symptoms in PwPD within the last 5-10 years. We expect that our project will generate data to explain:

(a) which is the most beneficial and/or best tolerated neurorehabilitation approach for dysphagic PwPD,

(b) the level and the extent of changes that can be promoted in this neurodegenerative population and

(c) whether there is heterogeneity in responses following neurorehabilitation.

The study will be placebo-controlled feasibility, cross-over study over 28 months, with two treatment arms for each patient: “real” and “sham” (placebo) of one of the three neurostimulation paradigms under investigation:

* Inhibitory rTMS (1Hz)
* Excitatory rTMS (5Hz)
* Pharyngeal Electrical Stimulation (PES)

# **Methodology**

All participants (n=66, please see power calculation below) should have a diagnosis of idiopathic PD within 5-10 ago (based on our published preliminary work).

## 5.1. Recruitment

Participants will be approached at neurology clinics in Greater Manchester by the medical team or the research nurses. Consultants Neurologists or Specialist Research Nurse responsible for the patient's medical care with access to the disease register of the patients in SRFT outpatient clinics, will be in position to review and comment on the suitability of the potential participants to the study.

Following identification of potential recruits, the Medical Team or research nurse will send an 'approach letter’ together with the Patient’s Information Sheet to the potential participant (or give a letter and information sheet if they are attending the outpatients’ clinic). The interested participants will contact the research team for further discussions. Information regarding the study will also be provided to the local PD UK branches meetings, where interested attendees can receive initial information. They will need to communicate with the research team to express their interest. The medical team will be informed and will need to review the medical notes of recruited PwPD from the community.

## **5.2. Summary of the activities**

Initially, the participants will visit the laboratories of GI sciences for 3 hours (day 1).

During Day 1, all participants will have extensive swallowing assessments, both qualitative (i.e. questionnaires) and quantitative {videofluoroscopy (VFS) at our Radiology Unit and neurophysiological assessments of swallowing neural network with TMS mapping, as per previous protocols (see procedures below)}. The formal assessment (VFS) will verify the severity of dysphagia. The initial screening and assessments will be followed by a single application of one of the treatments or the sham equivalent. The counter-part (real or sham) will be delivered a week later, as per randomisation (see below).

Following consent and screening, the participants will then be randomised to:

1. Inhibitory rTMS (1Hz)

2. Excitatory rTMS (5Hz)

3. Pharyngeal Electrical Stimulation (PES)

Randomisation will be delivered by one of the members of the research team. Randomisation will be set up on-line. The on-line randomisation software can be found here: <https://www.sealedenvelope.com/>

For the stratification of the participants in all arms, 2 factors will be used, namely: age and dysphagia severity. Dysphagia severity has been previously shown to be correlated to PD severity (as indicated by the different stages in the Hoehn & Yahr scale [[22](#_ENREF_22)]. Age (>75 years of age) is also another confounding factor that may increase the potential for developing dysphagia.

A second randomisation will be performed for the order of real or sham treatment across the two visits per participant. Follow-up assessments will be performed within 120 minutes of the application of treatment on both days. Therefore, all participants will participate over a period of 2 weeks and will come to the laboratories 2 times in total following consent. The participants will remain unaware of the randomisation throughout the study.

## **5.3. Consent**

The participants must be able to give informed consent and be easily transportable between the departments at Salford Royal NHS Hospital (being in a wheelchair will not prevent inclusion). An information sheet will be given to the participants prior to obtaining informed consent. They will also have the opportunity to discuss any queries before and during the study.

The consent process will be undertaken by research team members who will have up to date training in Good Clinical Practise. A member of the research team will provide the participant with the Participant information sheet. Simultaneously, the participant will be provided verbal information on the relevant aspects of the research. Sufficient time will be given to the patient to digest the written information (minimum of 24 hours). The researcher will return to the participant and their family to provide recap of the research aims, protocol, risks and contact details in order to check understanding of the potential participant. The standard consent form will be provided to the participant in order to obtain written consent. Throughout the research process, the researcher will check with the participant that he or she continues to give consent. In order to ensure that consent is provided by the participant is voluntary and fully informed; the following guidelines will be adhered to. The participant should:

1. Understand the purpose and nature of the research.

2. Understand what the research involves, its benefits (or lack of benefits), risks and burdens.

3. Understand the alternatives to taking part.

4. Be able to retain the information long enough to make an effective decision.

5. Be able to make a free choice and free of coercion.

6. Be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).

In case the participant, who has given informed consent, loses capacity to consent during the study, he/she will be withdrawn from the study. Identifiable data or tissue already collected with consent will be retained and used in the study. No further data or tissue will be collected or any other research procedures carried out on or in relation to the participant.

The volunteers will be invited to attend the laboratory prior to starting the study in order to familiarise themselves with the equipment and the procedures. The participants will receive reimbursement of their travel costs to and from Salford Royal NHS Hospital.

## **5.4.** Inclusion criteria

People diagnosed with Parkinson’s, aged 35-80 years old, who exhibit disability II-IV in Hoehn and Yahr Scale [[22](#_ENREF_22)] and have idiopathic PD according to UK PD Society Brain Bank [[23](#_ENREF_23)] will be reviewed by the medical team. The medical team will inform research team for the eligibility of the potential participant for the study. Verification of the presence and the severity of dysphagia will derive from formal assessments.

## **5.5.** Exclusion criteria

The exclusion criteria are: Supranuclear gaze palsy, cerebellar signs, prominent autonomic dysfunction, previous history of stroke, results in mini-mental state examination [[24](#_ENREF_24)] less than 24, gastro oesophageal surgery, head and neck cancer, untreated hypertension, metal in the throat or the head and history of seizures precluding TMS or pharyngeal catheter insertion. The aforementioned list is a result of careful review with the neurology team at Salford Royal Foundation Trust. If any of the first 7 exclusion criteria are present, dysphagia cannot be attributed solely to the existence of idiopathic PD. The last 3 exclusion criteria are safety precautions for neurophysiological and neurostimulation protocols below.

# **Experimental design and protocol**

**Inhibitory rTMS (1Hz)** The application of 1Hz rTMS will last approximately 10 minutes. Transcranial Magnetic Stimulation pulses will be delivered to the pharyngeal cortex with the largest motor evoked pharyngeal response (strong representation for pharyngeal musculature). The TMS coil will be positioned over the motor cortex [[15](#_ENREF_15), [16](#_ENREF_16)]. The equipment used, (stimulator: the Magstim Stimulation 2002 and coils: 70 mm figure of eight coils, Magstim Company, Whitland, Wales) are housed at the GI Sciences Laboratories at SRFT.

**Excitatory rTMS (5Hz)** The application of 5Hz rTMS will last approximately 10 minutes and will be delivered to the pharyngeal cortex with the largest motor evoked pharyngeal response with a TMS coil positioned over the motor cortex [[16](#_ENREF_16), [17](#_ENREF_17)]. The equipment used, (stimulator: the Magstim Stimulation 2002 and coils: 70 mm figure of eight coils, Magstim Company, Whitland, Wales) are housed at the GI Sciences Laboratories at SRFT.

**Pharyngeal Electrical Stimulation (PES)** The application of PES at 5Hz will last approximately 10 minutes and will be delivered with an intraluminal catheter positioned through the nose or mouth. Subjects will be required to allow the insertion of a 3.2 mm diameter intraluminal catheter (Gaeltec Ltd, Dunvegan, Isle of Skye) either transnasally. The catheter house a pair of bipolar platinum ring electrodes that are positioned in the hypopharyngeal area with manometric procedures [[19-21](#_ENREF_19)] to record electromyographic (EMG) traces. An earth wire will be connected to a skin electrode sited over the upper part of one of the sternocleidomastoid muscles in the neck. The catheter will be connected via a preamplifier (Cambridge Electronic Design Ltd, Cambridge), amplifier (CED 1902) and interface (CED 1401) to a personal computer which allows real time visualization and recording of the traces using Signal Application Program (Cambridge Electronic Design Ltd, Cambridge). This has filters set at 200 Hz to 2 kHz and allows a sampling rate of 4-8 kHz. Analysis of the amplitude and latencies of the traces will be conducted using Signal programs. The PES is delivered through the catheter when this is connected to an electrical stimulator (Digitimer model DS7, Welwyn-Garden City, Herts, United Kingdom) and a trigger generator (Digitimer Neurology system) allowing measurements of an individual’s sensory and maximal thresholds. With this technique we can record the sensory and maximal thresholds.

Sensory threshold is defined as the first perceptible sensation of electrical stimulation and is calculated as the average of 3 trials. On each trial, stepwise increments of approximately 0.1mA per second will be instigated starting at zero stimulator output. The maximum tolerated intensity will be determined in an identical manner but this time the subject will be asked to identify the point when the stimulation becomes uncomfortable. The intensity of pharyngeal stimulation is then set at 75% of the difference between the two. With the stimulation parameters determined as above, the pharyngeal stimulation will be delivered at a frequency of 5Hz for 10 minutes.

The intensity of the peripheral stimulus will be determined according to the formula:

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Peripheral Stimulation Intensity | = | Sensory Threshold | + | 0.75 | x | Discomfort Threshold | – | Sensory Threshold |

* Sensory threshold = Lowest current that is discernible by the subject
* Discomfort threshold = Highest current tolerated by the subject

**Procedures (See are explained at the end of the protocol):** The screening will include gathering medical notes and swallowing screening with the Swallowing Disturbances Questionnaire [[25](#_ENREF_25)] and Swallowing Quality of Life Questionnaire (SWAL-QOL) [[26](#_ENREF_26)], together with Hospital Anxiety and Depression Scale (HADS) [[27](#_ENREF_27)] questionnaire and PD specific screening, such as non-motor PD UK [[28](#_ENREF_28)]. Previous formal assessments of swallowing on the participants will be retrieved at this stage. All other assessments (below) will be performed before and after real and sham paradigms. The neurophysiological measurements will take place at baseline and then be performed immediately after the treatment and after VFS.

*Swallowing assessments:*

1) Videofluoroscopy (Protocol in the Appendix)

2) Saliva frequency Rate [[29](#_ENREF_29)]

*PD specific assessments:*

3) Movement Disorders Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [[30](#_ENREF_30)]

*Neurophysiological assessments:*

4) Cortical TMS mapping and trigeminal pathway excitability [[2](#_ENREF_2)]

**Primary Outcome measure compared to sham counterpart:**

Change in penetration-aspiration (PA) scores on videofluoroscopy [[31](#_ENREF_31)] immediately post Interventions

**Secondary Outcome measures:**

1. Single Score-Saliva frequency Rate, residue on VFS, number of clearing swallows

2. Single Score and within subcategories of- MDS-UPDRS post interventions

3. Change in the amplitude pharyngeal motor evoked potential (as a measure of excitability) from cortical TMS mapping and trigeminal stimulation post interventions.

# **Statistical method**

The primary analysis will be on PA scores post-real compared to PA scores following sham. Analysis will be conducted with a multilevel linear regression model with the scores from the swallows used as the dependent variable and the scores in the treatment arm will be included as a factor in the model. Inference will be based on the significance of the treatment arm parameter using a likelihood ratio test. Secondary analysis will consist of multilevel regression of the other outcomes after real and sham stimulation. A 5% significance level will be used. Additionally, correlations between the several measurements (swallowing questionnaire and PD severity, PD specific questionnaires etc.) will be performed using Pearson correlation coefficients. Results will be corrected with Holms-Sidak step-down technique to correct for multiple comparisons and correlations.

**Power calculation – sample size**

In the literature the primary outcome measure used extensively is the change in PA scores. This is the first time that these treatments will be compared directly in PwPD. Previously we have seen an average improvement of penetration-aspiration scores of 2.7 (±0.2, SD: standard deviation) points on a swallow scale with real neurostimulation in 12 chronic dysphagic stroke patients while an improvement of an average of 1 (±0.25, SD) point with sham neurostimulation. Within-patient residual standard deviation was estimated as 1.25. Between-patient residual standard deviation was estimated as 0.3. The minimum clinically important difference was decided to be 1 point on the PA scale, as this is the smallest increment on the scale. The estimated regression coefficients for the intercept and the mean of six baseline PA scores were used in the simulation. Study data were simulated 10,000 times and the likelihood ratio test was used to make inference on the treatment parameter. The treatment parameter was significant in over 9900 out of 10,000 simulations. Twenty PwPD per arm therefore will give me 99% power to detect a difference of 1 point between arms using the proposed analysis. Therefore, there will be a total of 66 PwPD recruited, 22 in each intervention arm, to allow for subject drop out.

# **Methods & Assessments with details (alphabetical order)**

**Movement Disorders Society-Unified Parkinson’s disease Rating Scale [**[**30**](#_ENREF_30)**] (APPENDIX F- separate document)**: a modified version of the rating scale used to follow the longitudinal course of PD. Interview and clinical observation evaluate the following:(1)non-motor experiences of daily living, (2)motor experiences of daily living, (3)motor examination and (4)motor complications. Each subscale has 0-4 ratings, where 0=normal, 1=slight, 2=mild, 3=moderate, and 4=severe.

**Non-motor symptoms Questionnaire [**[**28**](#_ENREF_28)**] (APPENDIX D- separate document)**: a 30-item questionnaire to review the non-motor symptoms of PwPD, with yes/no answer for the trueness of the statement during the past month.

**Pharyngeal Electrical Stimulation [**[**19-21**](#_ENREF_19)**]:** has been extensively investigated in health and in stroke and has proven to be a safe non-invasive therapeutic approach; showing immediate beneficial effects in swallowing safety and performance in stroke patients, and resulted in reduced time to hospital discharge and functional swallowing in acute stroke patients.

For the **Sham PES** the intraluminal catheter is in situ, but no stimulation was delivered, as per previous studies.

**Repetitive Transcranial Magnetic Stimulation: Low frequency [**[**15**](#_ENREF_15)**]:** trains of stimuli will be delivered through the figure-of-8 coil connected to a Magstim super rapid stimulator (Magstim Co). One Hz repetitive TMS at 120% of pharyngeal motor threshold will be delivered for 10 minutes with 600 single pulses, as previously described. **High Frequency [**[**16**](#_ENREF_16)**,** [**17**](#_ENREF_17)**,** [**21**](#_ENREF_21)**]:** Trains of stimuli will be delivered to pharyngeal motor cortex with the TMS coil (Magstim, Wales, UK). The optimal parameters for high frequency rTMS will be frequency of 5Hz, intensity 90% of resting thenar Motor Threshold (MT) in train of 250 pulses, in 5 blocks of 50 with 10s between-blocks pause.

**Sham stimulation [**[**15**](#_ENREF_15)**,** [**16**](#_ENREF_16)**,** [**21**](#_ENREF_21)**]:** (for both low and high frequency rTMS) will be given using a 90° coil tilt, which produces the same noise as active stimulation but has been shown not to produce motor cortical stimulation. Each sham treatment will be delivered with the same clicking noises as the counterpart (600 pulses for low and 250 for high frequency rTMS).

**Swallowing Disturbance Questionnaire [**[**25**](#_ENREF_25)**] (APPENDIX B)**: a validated questionnaire of 15 questions on symptoms in swallowing. PwPD indicate whether the symptoms appear: never (scored with 0), seldom (1), frequently (2), and very frequently (3). A score of more than 11.5 indicates the need for further assessments.

**The Hospital Anxiety and depression scale (HADS) [**[**32**](#_ENREF_32)**]** **(APPENDIX E)** used to determine the levels of anxiety and depression that a patient is experiencing. The HADS is a fourteen item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression.

**Swallowing Quality-of-Life Questionnaire (Swal-QoL) [**[**26**](#_ENREF_26)**] (APPENDIX G- separate documentation)**: a questionnaire with 44 questions for the 11 domains: Burden, Eating, Desire, Eating duration, Symptoms, Food Selection, Communication, Fear, Mental Health, Social, Fatigue, Sleep. The lower score, the more reduced is the quality-of-life of the participant.

**Transcranial Magnetic Stimulation**: Electromyographic (EMG) responses from the pharynx will be recorded via ring electrodes built into an inserted 3mm diameter intraluminal catheter routinely inserted transnasally through the participant’s nostril. Single pulse TMS will be used to non-invasively study bilateral swallowing musculature cortico-bulbar pathways and measure cortical excitability through changes and pharyngeal EMG. As *additional control*, we will measure the excitability of the cortical representation for hand musculature and median nerve, by measuring the change in the EMG activity as recorded via electrodes attached to the thenar and median nerve.

*Brainstem Reflexes*: Any potential changes in brainstem reflexes, will be measured with trigeminal nerve stimulation performed with a smaller figure-of-eight TMS coil placed over the right supraorbital region of the face.

**Videofluoroscopy (APPENDIX C):** the research VFS includes swallowing 10 liquid boluses of 5ml water mixed with barium sulphate (E-Z-Paque, UK) at a concentration of 60% w/v, 3 boluses of paste consistency mixed with barium sulphate and 3 swallows of ¼ of a biscuit coated with liquid barium sulphate and two swallows of 50 ml of water mixed with barium sulphate.

In total, the participants will swallow 18 times before and after the treatments on each of the two days that will participate in the trial. The procedure will be stopped if a patient shows significant signs of swallow compromise (i.e. severe aspiration of more than 50% of the boluses in 3 consecutive swallows), according to the widely accepted 'safety protocol'. Images are captured digitally for off-line frame-by-frame analysis. Evaluation of swallowing safety is determined with a validated 8-point PA scale **(APPENDIX A)** [[31](#_ENREF_31)].

**Spontaneous Saliva Swallowing Frequency:** We will measure the rate of spontaneous saliva swallowing frequency before and after the treatments. The participants will relax on a chair for 30 minutes and a pair of electrodes will be attached around the area of the neck muscles. The electrodes (single use – Ambu Neuroline 715, Ambu, Denmark) will stay for 30 minutes in place and will be discarded thereafter. The spontaneous saliva swallowing frequency will be performed at baseline and after the treatments on both days.

# ****Trial Coordination & Reporting of adverse events****

From the initiation of the trial, a Data Monitoring Committee (DMC) and a Trial Steering Group (TSG) will be formed in order to, according to [MRC Guidelines for GCP for Clinical Trials 1998](http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/):

DMC: assess at intervals, the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. The DMC will meet before the trial, then at 6 months, 18 months and when the study is completed.

TSG: monitor the trial progress and to conduct and to advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC. The members will be independent of the investigators, their employing organisations, funders and sponsors and patient and public involvement is also guaranteed. An invitation will be send to appropriate people at the commencement of the trial. The TSC will meet before trial commences, at 6 months, 12 months, 18 months and at the end of the trial.

A suspected adverse event such as clinical deterioration of a patient following videofluoroscopy as a possible association after aspirating barium into the lungs will firstly be reported to the Chief Investigator and the relevant Principal Investigator of the site where patient was recruited from. However, it is unlikely that participation to the study will result in any deterioration of the disease course. The sponsor of the study, the University of Manchester will also be notified in writing. If an event is regarded as a serious adverse event (SAE), the standard SAE reporting form issued by the National Patient Safety Agency will be completed and sent to the relevant research ethics committee that provided the favourable ethical approval.

# **Summary of the study**

Consent Form

Baseline TMS mapping of the swallowing motor cortex

Baseline measurements including (MDS-UPDRS, Non-motor symptoms Questionnaire, SDQ, HADS, Swal-QoL, Spontaneous Saliva swallowing Frequency)

Baseline videofluoroscopy

Repeat videofluoroscopy

Randomisation into one of the following:

Repeat TMS mapping of the swallowing motor cortex

End of the study

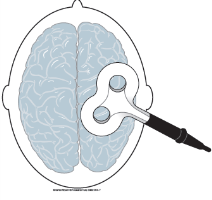
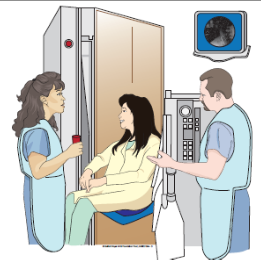
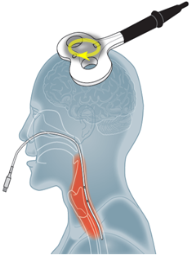
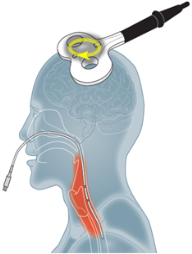
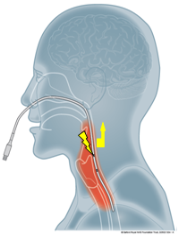
Repeat assessments including Non-motor symptoms Questionnaire, SDQ and spontaneous Saliva swallowing Frequency

Pharyngeal Electrical Stimulation

1Hz

Repetitive TMS

5Hz Repetitive TMS



Repeat TMS mapping of the swallowing motor cortex

# **Appendices (some questionnaires are attached to the IRAS form, due to the numerous pages these occupy)**

1. **The Penetration Aspiration Scale [**[**31**](#_ENREF_31)**]**

|  |  |
| --- | --- |
| **1** | Material does not enter airway |
| **2** | Material enters airway.  Remains above vocal cords & is ejected from airway |
| **3** | Material is above vocal cords & is not ejected from airway |
| **4** | Material enters airway, contacts vocal cords & ejected from airway |
| **5** | Material contacts the vocal cords & is not ejected from airway |
| **6** | Material passes below the vocal cords & is ejected into larynx or out of airway |
| **7** | Material passes below the vocal cords & is not ejected from the trachea despite effort |
| **8** | Material enters airway, passes below the vocal cords & no effort is made to eject the material |

1. **Swallowing Disturbance Questionnaire**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Questions** | **0** | **1** | **2** | **3** |
| **Never** | **Seldom (once a month or less)** | **Frequently (1-7 times a week)** | **Very frequently (more than 7 times a week)** |
| 1. Do you experience difficulty chewing solid food like an apple, cookie or a cracker? |  |  |  |  |
| 2. Are there any food residues in your mouth, cheeks, under the tongue or stuck to the palate after swallowing? |  |  |  |  |
| 3. Does food or liquid come out of your nose when you eat or drink? |  |  |  |  |
| 4. Does chewed up food dribble from your mouth? |  |  |  |  |
| 5. Do you feel you have too much saliva in your mouth; do you drool or have difficulty swallowing your saliva? |  |  |  |  |
| 6. Do you swallow chewed up food several times before it goes down your throat? |  |  |  |  |
| 7. Do you experience difficulty in swallowing solid food (i.e. do apples or crackers get stuck in your throat? |  |  |  |  |
| 8. Do you experience difficulty in swallowing pureed food? |  |  |  |  |
| 9. While eating, do you feel as if a lump of food is stuck in your throat? |  |  |  |  |
| 10. Do you cough while swallowing liquids? |  |  |  |  |
| 11. Do you cough while swallowing solid foods? |  |  |  |  |
| 12. Immediately after eating or drinking, do you experience a change in your voice, such as hoarseness or reduced volume? |  |  |  |  |
| 13. Other than during meals, do you experience coughing or difficulty breathing as a result of saliva entering your windpipe? |  |  |  |  |
| 14. Do you experience difficulty in breathing during meals? |  |  |  |  |
| 15. Have you suffered from a respiratory infection (pneumonia, bronchitis) during the past year? | Yes | No |  |  |

1. **Videofluoroscopy Protocol**

|  |  |
| --- | --- |
| Liquid Swallowing | 60% w/v E-Z-Paque |
| 1. | 5 ml |
| 2. | 5 ml |
| 3. | 5 ml |
| 4. | 5 ml |
| 5. | 5 ml |
| 6. | 5 ml |
| 7. | 5 ml |
| 8. | 5 ml |
| 9. | 5 ml |
| 10. | 5 ml |
|  |  |
| Pudding Texture Swallowing | 40% w/v E-Z-Paque |
| 1. | 5 ml |
| 2. | 5 ml |
| 3. | 5 ml |
|  |  |
| Hard Bolus Swallowing | ¼ Digestive Biscuit coated with Liquid Barium |
| 1. | ¼ |
| 2. | ¼ |
| 3. | ¼ l |
|  |  |
| Sequential Swallowing |  |
| Liquid Swallowing | 60% w/v E-Z-Paque |
| 1. | 50 ml |
| 2. | 50 ml |

1. **Non-motor Symptoms in Parkinson ’s disease**





1. **Hospital Anxiety and Depression Scale**



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