# An exploration of the application of non-invasive cerebellar stimulation in the neuro-rehabilitation of dysphagia after stroke (EXCITES).

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## Abstract

**Background:** Dysphagia is a common, serious complication post-stroke. A number of treatments exist, but a lack of high-quality evidence limits guidance for clinicians and commissioning bodies, resulting in an ongoing reliance on compensatory management. Repetitive transcranial magnetic resonance stimulation (rTMS) targeting the cerebellum, is a non-invasive brain stimulation technique requiring minimal physical or cognitive input from the patient, and has been shown to induce positive brain changes in physiological studies as measured by increased cortical excitability. **Aim:** To explore: i) the feasibility and immediate effect, ii) the optimal dose for long-term effect, of cerebellar rTMS in patients with dysphagia in acute/sub-acute stroke. **Methods:** A two-phase, double blinded, randomised control trial. Participants will be recruited from stroke units in Nottingham and Salford. Dysphagia will be confirmed via baseline Videofluoroscopy (VFS). Participants will be blinded to subgroup: i) single treatment of (10Hz, 250 pulse) cerebellar rTMS or sham stimulation, ii) cerebellar rTMS daily for 3 days, twice-daily for 5 days, or twice-daily sham treatment for 5 days. **Results:** Severity of dysphagia will be assessed with VFS, using the penetration aspiration scale (PAS): i) one-hour, ii) two-weeks, post-treatment. Additional comparative measures will be taken from: i) pharyngeal motor evoked potential (MEP) amplitudes, ii) the Functional Oral Intake Score (FOIS) and Dysphagia Severity Ratings Scale (DSRS). **Conclusion:** By demonstrating feasibility and optimal dosing this study is potentially a further step in the translational development of cerebellar rTMS as a treatment for post-stroke dysphagia, leading to a definitive phase 3 efficacy trial.

## Background

The incidence of oropharyngeal dysphagia (OPD) (impairment to the oral and/or pharyngeal phases of swallowing) following stroke ranges from 37-78% [1]. Pneumonia has been reported as the most common, serious medical event following stroke, with OPD related aspiration accounting for 60% of cases [2]. Pneumonia impacts on patient recovery and subsequent adverse effects on length of inpatient stay, morbidity and mortality [3]. Surviving patients with OPD are significantly more likely to require a skilled nursing facility on discharge, with subsequent impact to long-term health costs and wellbeing [4]. Psychologically and socially, OPD has been shown to adversely affect an individual's enjoyment of food, negatively impacting their perceived quality of life [5].

Recent Cochrane reviews of post stroke dysphagia management have shown that cortical rTMS may have a positive effect on swallowing ability, but does not appear to have any effect on mortality [6]. When taken together, swallowing therapies provide no significant beneficial effect on death, dependency or disability [7]. However, the variable quality of research, small number of studies, and lack of homogeneity in methods, means that the potential improvements to pertinent variables, such as hospital length of stay and swallowing function, are yet to be demonstrated [7]. There is a clear need for further, high quality, objective research of individual techniques to determine their potential benefits. Research into non-invasive brain stimulation and swallow function is promising due to the reduced need for complex patient physical or cognitive engagement, and the potential for relatively short courses of treatment.

Non-invasive cerebellar stimulation aims to enhance motor plasticity in the swallowing cortex after stroke. We have shown that the human cerebellum is strongly activated during the act of swallowing [8] and, when stimulated with single TMS pulses, can strongly facilitate the corticobulbar projection to the pharynx in humans[9]. We have identified the most relevant frequency of stimulation of the cerebellum (10Hz) that can produce longer term excitation in the human swallowing motor system [10]. We believe that the potential for improving swallowing with cerebellar stimulation is much greater than other methods. Our previous work has shown that the recovery of swallowing function, relies on increased excitability in intact projections from the non-stroke hemisphere [11]. With cerebellar stimulation producing some of the greatest levels of corticobulbar excitation that we have described so far [9]. The human cerebellum is also a more pragmatic target for therapeutic neuro-rehabilitation, as it is relatively easy to locate and stimulate, and has reduced risk of inducing unwanted effects (such as kindling and seizures).

A final factor relates to a "virtual lesion" model of swallowing dysfunction in healthy volunteers. This involves low frequency (1 Hz) rTMS targeted at the 'dominant' cortical pharyngeal representation. This results in temporary suppressive changes to pharyngeal motor evoked potential amplitudes, and changes to swallowing behaviour. These changes have been shown to be similar to those seen in patients with post stroke dysphagia [12]. We have demonstrated that 'virtual lesions' can be reversed quite successfully with neuro-stimulation techniques including: cortical rTMS and cerebellar rTMS [13, 14]. Our recent work demonstrated that this result can be achieved irrespective of which side of the cerebellum is stimulated [15]. Results from previous virtual lesion studies have translated into observable changes in swallowing ability in patients with post stroke dysphagia[16].

**Overarching Hypothesis**
Cerebellar targeted rTMS will reduce the severity of dysphagia post stroke.

**Aims**
We aim to use cerebellar rTMS to:

Study 1

- Demonstrate the feasibility of its use in patients with OPD post-stroke.
- Increase the amplitude of pharyngeal cortical motor evoked potentials (MEPs) in patients with post stroke dysphagia.
- Improve swallowing function – as assessed using videofluoroscopy (VFS) – in patients with post stroke dysphagia.

Study 2

- Obtain information as to the optimum cerebellar rTMS dosing regimen needed to induce lasting improvements in swallowing function – as assessed using VFS and functional outcome measures – in patients with post stroke dysphagia.

**Ethical Approval**
Ethical approval for the study was granted by Greater Manchester South NHS research ethics committee (18/NM/0232).

**Methods**
EXCITES is a randomised, double blinded (with subgroup and outcome assessor blinding), sham-controlled study. The study aims to evaluate the feasibility and efficacy of 10Hz excitatory cerebellar rTMS in improving dysphagia in acute/subacute stroke. It has a two-part design and will be conducted in the Northern Care Alliance (Salford Royal Hospital NHS Trust and Pennine Acute Hospitals NHS Trust) and Nottingham City Hospital. The basic study design for both trials is summarised in figure 1.

**Patient population**
72 medically stable patients with post stroke dysphagia will be recruited from approved Hospitals across the two trusts. 24 patients will be recruited for the first part of the study and 48 for the second. A 50% division of recruitment is planned between Manchester and Nottingham but actual numbers may vary.

**Inclusion criteria**
- Confirmed anterior or posterior circulation stroke
- ≤12 weeks post ictus
- Adults ≥18 years with no maximum age
- Medically stable
- Dysphagic

**Exclusion criteria**
- Advanced dementia (judged to impair compliance with protocol).
- Other neurological conditions that may explain dysphagia.
- Previous history of dysphagia.
- Presence of implanted cardiac pacemaker or defibrillator.
- A diagnosis other than stroke is suspected (e.g. brain tumour).
- Severe concomitant chronic medical condition that compromises cardiac or respiratory status.
- Significant structural abnormalities of the mouth or throat.
- Patients with ongoing lower respiratory tract infection requiring either antibiotics or oxygen.

**Recruitment**
Potential participants with strokes who fulfil the inclusion criteria will be approached on stroke units, rehabilitation units or general medical wards. Participants will remain under the care of their medical teams at all times during the study. Initial recruitment will be undertaken by a research fellow and/or health care professional (medical doctor, research nurse or speech and language therapist). Patients and their family members will be supported to understand all trial information and given adequate time to consider the research before giving written consent. Whenever possible, participants who have capacity to give consent will be recruited.

**Capacity**
The researchers will make every effort to ensure that potential participants recruited for this study have the capacity to give informed consent. Additionally, on the rare occasions that participants lose capacity during the study, their participation will be

delayed in order to give them time to recover from any temporary loss of capacity as long as inclusion criteria are maintained. Only participants who are able to provide consent themselves will be recruited.

**Randomisation**
Randomisation will be performed by a bespoke computer database designed for EXCITES. Members of the research team who encounter patients as part of their role will have no control over the process of randomisation.

**Blinding**
Participants will be blinded to whether they are receiving 10Hz rTMS or sham treatment. Baseline assessment, randomisation and the treatment phase will be carried out by a single researcher in each site. Post treatment phase PAS will be scored from a DVD by an assessor blinded to sub-group.

**Interventions**

**Electromyography (EMG)**
Study 1.
EMG recordings will be taken at baseline and at 1-hour post treatment from sensors in the pharynx and on the thenar of the thumb.

Pharyngeal: Pharyngeal motor evoked potentials (MEPs) will be recorded in response to TMS of the swallowing motor cortex using a thin intra-luminal EMG catheter (Gaeltec Ltd, UK), positioned in the pharynx. Catheters will be inserted into the pharynx via either the nostrils or the mouth depending on participant preference. To ensure correct pharyngeal placement, catheters will be positioned at a distance of 13-15cm from the entrance to the nostrils or the mouth to the location of their electrodes. After placement electromyography recordings can be visualised on the Signalsoft program and used to confirm placement.

Thenar: Thenar cortical representation resting membrane thresholds and motor evoked potentials will be recorded using skin electrodes (H69P, Tyco Healthcare, Gosport, UK) attached to the abductor pollicis brevis on the side of the undamaged cortical hemisphere.

**Cortical and cerebellar TMS**

Study 1.
Single pulse TMS will be delivered using a figure of eight coil (Magstim Company, Whitland, Wales, UK). It will be used to establish the location and resting motor thresholds of pharyngeal ‘hotspots’ over the cortex and cerebellum and thenar ‘hotspots’ over the cortex. Once cortical and cerebellar mapping has been completed TMS will be used to measure pharyngeal and thenar motor evoked potentials.

**Cerebellar rTMS**
Study 1 and 2.
Cerebellar stimulation will be delivered with repetitive TMS (rTMS) (Super-rapid, Magstim Co. UK). 250 pulses at 10 Hz of cerebellar rTMS will be delivered at an

intensity of 90% of the thenar resting membrane threshold to ensure safe delivery of rTMS [9, 10].

**Videofluoroscopy (VFS)**

Study 1 and 2.

VFS will be employed to assess swallowing behaviour, using a Siemens Fluorospot® H Sireskop SX Unit (Siemens Medical Engineering, Germany). Quantitative measurements of oropharyngeal bolus flow and aspiration will be made on six consecutive swallows of thin fluid. VFS involves a radiation dose in the region of 1.5-3.0 mSv. Analysis of bolus movement will be made by trained speech and language therapy professionals. Participants recruited as part of the study will receive two sessions of VFS in total, a baseline assessment before any intervention and a comparative outcome assessment afterwards.

The VFS protocol for this study involves the participant swallowing 6 boluses of 5mls of water mixed with barium sulphate (E-Z Paque, UK) presented via a spoon. This will be mixed to a concentration of 60% water and 40% barium equating to 'thin' fluid viscosity.

In total, participants will be asked to swallow 12 times before and after rTMS. VFS will be stopped if there is significant compromise to swallowing. We define this as aspiration passing and remaining below the level of the vocal cords (penetration aspiration scale (PAS) score of 7/8) in 3 consecutive swallows. The 7-point PAS (1-8) reflects the furthest level bolus matter enters into the airway [17]. To establish the inclusion criteria of OPD, PAS scores will be taken from live images of the trials within the baseline VFS. For the purposes of this study, a score of $\geq$3 in at least 3 of the 6 trials (or where there is significant compromise) is defined as OPD.

**Design**

Study 1

This study sets out to generate data to answer the question:

Can non-invasive cerebellar stimulation produce short term improvements in swallowing after acute stroke?

24 participants with post stroke dysphagia will be recruited from the stroke wards of approved hospitals using the inclusion and exclusion criteria detailed above. Participants will be randomly divided to create two groups of 12 patients receiving either cerebellar rTMS (10Hz, 250 pulses), or sham. Cerebellar rTMS will be delivered to marked cerebellar areas by holding the figure of eight TMS coil flat against the scalp with its handle pointing superiorly. Sham stimulation will be administered by holding the figure of eight TMS coil perpendicular to the scalp with one of its 'wings' touching the patient and its handle pointed superiorly. In this circumstance, patients will hear the click of each pulse being delivered and will feel pressure on the back of their head but will not receive any stimulation to their cerebellum. This technique has been used in other studies by our research group[10]. Participants will have surgical caps placed over their heads, secured with tape to enable pharyngeal and thenar hotspots to be marked. Single pulse TMS will

be used to locate pharyngeal and thenar hotspots over the cortex and pharyngeal hotspots over the cerebellum. TMS will also be used to establish resting motor thresholds from these hotspots. Resting motor thresholds are defined as the minimum intensity of targeted TMS stimulation needed to cause pharyngeal MEPs of >20 μV in 5 out of 10 trials or thenar MEPs of >50 μV in 5 out of 10 trials. 250 pulses at 10 Hz will be delivered over cerebellar pharyngeal hotspots.

Participants will have VFS pre and post cerebellar rTMS to measure their PAS. In addition, participants will be intubated with a pharyngeal EMG catheter for pre and post recordings of pharyngeal motor evoked potentials (MEPs) to cortical TMS.

Study 2
This study aims to identify the optimal dose of TMS needed to improve dysphagia over a longer period of time, addressing the question:

What is the optimal regimen for longer term swallowing improvement?

48 dysphagic participants who fulfil the inclusion and exclusion criteria will be recruited. They will be randomly divided into 3 groups of 16 patients. As it is not known how the cerebellar stimulation method should be delivered to patients, a dose ranging treatment trial will be performed. Group A will receive low level stimulation; group B high level stimulation and group C sham stimulation. From our previous work with pharyngeal stimulation [18], we propose that group A will receive stimulation once per day for 3 days. Group B will receive stimulation twice per day for 5 days. Group C will receive sham stimulation (delivered as in study 1) twice a day for 5 days. Groups A and B will receive cerebellar rTMS at the same intensity as in study 1 (10Hz, 250 pulses), but all groups will also receive standard speech and language therapy as part of their normal care.

**Study outcomes**

Study 1
Comparative PAS will be calculated via VFS at baseline (pre-randomisation) and at 1 hour; specifically, the number of swallows out of six assessed that achieve a PAS of 3 or more. PAS will be assessed via frame-by-frame analysis of DVD recordings of the VFS procedures by an assessor blinded to treatment group. Selected swallow timings will also be measured in post-assessment VFS analysis as an adjunct to PAS in determining any potential change to swallow function. Pharyngeal MEP amplitude pre and at 1 hour will also be recorded.

Study 2
PAS will be calculated via VFS at baseline and at 2-week assessment. For the second study we will include functional outcome scores alongside VFS. The Functional oral ingestion scale (FOIS) and the dysphagia severity rating scale (DSRS) will be conducted by a member of the research team at baseline and at 2 weeks. These factors will thus determine the regimen of cerebellar stimulation that leads to the greatest improvement in swallowing performance as a prelude to a phase IIb/III RCT.

**Management of adverse events**
Adverse events of chest infection will be recorded where clinician-initiated antibiotics for lower respiratory tract infection is recorded. Due to the fact that all interventions will take place within NHS hospitals, numerous medical staff will be on hand to provide assistance in the event of any adverse event. In addition, individuals performing all the interventions (TMS and VFS) and assessments will be clinically trained members of staff with up to date basic life support qualifications.

Adverse events with TMS include headaches, facial twitching, syncope and seizures. The risk of seizures with TMS is <0.1% [19]. Risks with the use of VFS include exposure to ionising radiation and aspiration (when small radio-opaque boluses are being swallowed). VFS is widely used in the NHS for the objective assessment of swallowing function in patients with strokes and the protocols will comply with local risk management.

**Sample size**

Based on earlier pharyngeal stimulation studies we observed mean improvement (SD) of 1.8 (1.77) swallows out of six scoring as problematic (3 or more on the penetration-aspiration scale - see additional data) in the treated group, compared with a deterioration of 0.6 (1.56) swallows in the controls. Considering the feasibility and proof of concept nature of this phase of the proposal (question 2, protocols I and II) in stroke patients, we estimate that the 2 protocols will require 24 and 48 patients, respectively.

**Results**
Recruitment has not yet begun; example summary tables for expected results are presented. In practice, all data fields will be captured for each participant.

**Data analysis**
In both studies, the unpaired baseline and outcome data will be analysed via the Mann-Whitney U test to establish the effect of cerebellar rTMS on PAS and MEP.

**Data management**
All acquired data will comply with research governance and ethics regulations and follow EU and MRC guidelines. All acquired data will be coded, anonymised and stored on University of Manchester and Nottingham servers maintained by a local IT services team.

**Discussion**
This paper presents the protocol for the EXCITES study of cerebellar rTMS in post-stroke dysphagia, which aims to establish the feasibility of this technique within the stroke population and explore its practical implementation. Feasibility will be established through tolerance of the procedure by patients in the sub-acute phase of stroke recovery, alongside its successful implementation within a working ward and videofluoroscopy suite environment. Establishing feasibility and any immediate short-term changes to aspiration and cortical excitation will enable progression to the second, dose-ranging, phase of the trial to establish the most effective practical application of the technique. Should the outcomes be positive, this research will lead to further large-scale trials of efficacy, following the established design of previous

treatments, such as Pharyngeal Electrical Stimulation [22]. This technique could offer a ward-based treatment which demands minimal cognitive and physical engagement from the patient, and could have significant impact on the clinical management of dysphagia in the future.


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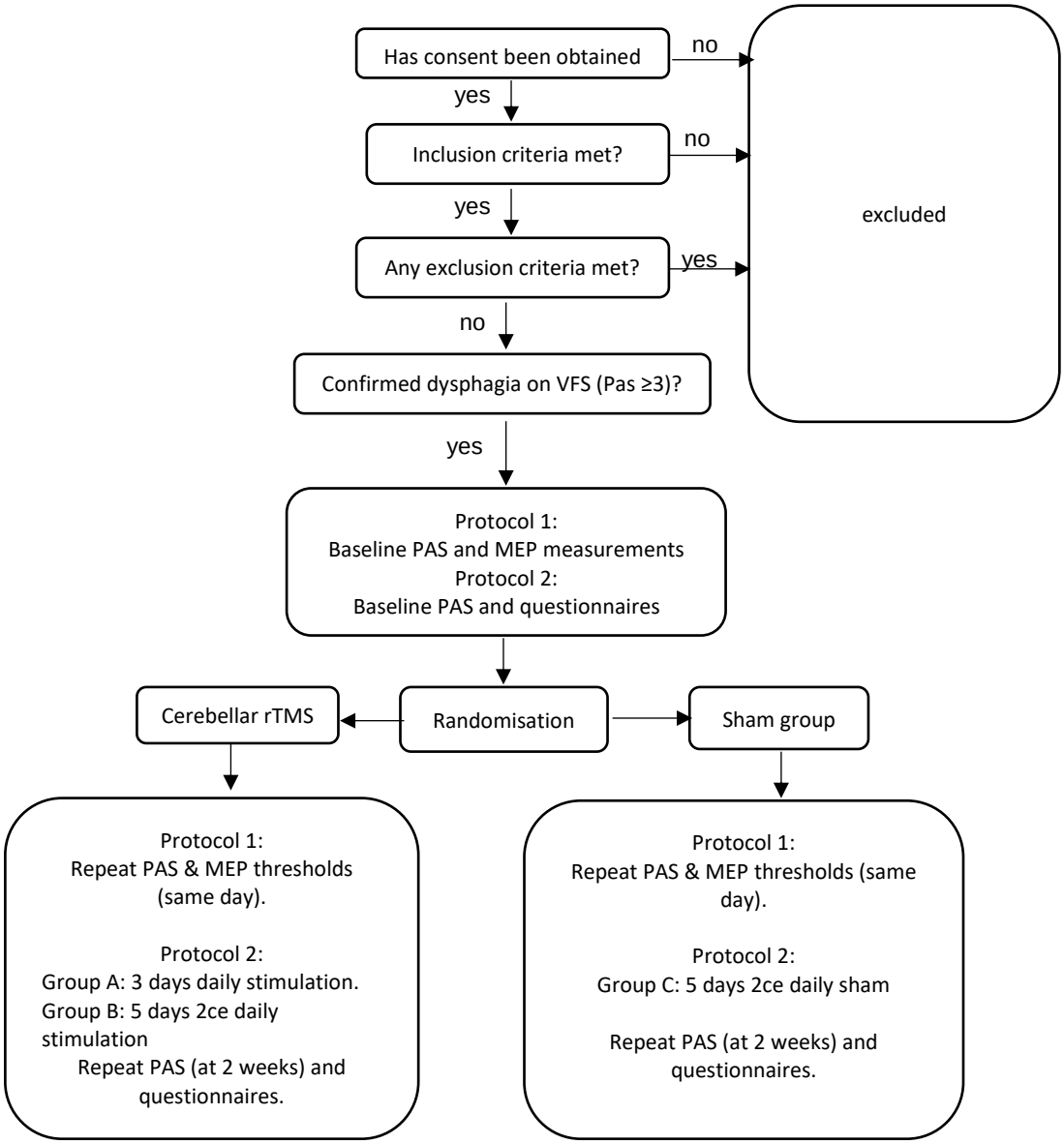


*Figure 1. Recruitment flow*

Table 1. Baseline Characteristics Study 1

| | **Active (n=12)** | **Sham (n=12)** |
|---|---|---|
| Age, y | M [IQR] | M [IQR] |
| NIHSS | M [IQR] | M [IQR] |
| Barthel | M [IQR] | M [IQR] |
| Time to Randomisation post stroke | M [IQR] | M [IQR] |
| DSRS on entry | M [IQR] | M [IQR] |
| PAS on entry | M [IQR] | M [IQR] |
| MEP on entry | M [IQR] | M [IQR] |

Table 2. Comparison of change in primary outcome measures Study 1

| | **Active** | **Sham** | **DIM** | **2p** |
|---|---|---|---|---|
| PAS | M [IQR] | M [IQR] | MWU | |
| MEP | M [IQR] | M [IQR] | MWU | |

DIM: difference in medians; MWU: Mann-Whitney

Table 3 Adverse events and Withdrawal Study 1

| | **Active (n=12)** | **Sham (n=12)** |
|---|---|---|
| CI during admission | M [IQR] | M [IQR] |
| In hospital mortality | N (%) | N (%) |
| SAE | N (%) | N (%) |
| Death | N (%) | N (%) |
| Withdrawals | N (%) | N (%) |

CI: Chest infection
SAE: Serious adverse event

Table 4 Characteristics Study 2

| | **Group A Once daily (n=16)** | **Group B Twice daily (n=16)** | **Group C Sham (n=16)** |
|---|---|---|---|
| Age, y | M [IQR] | M [IQR] | M [IQR] |
| NIHSS | M [IQR] | M [IQR] | M [IQR] |
| Barthel | M [IQR] | M [IQR] | M [IQR] |
| Time to randomisation post stroke | M [IQR] | M [IQR] | M [IQR] |
| DSRS on entry | M [IQR] | M [IQR] | M [IQR] |
| FOIS on entry | M [IQR] | M [IQR] | M [IQR] |
| PAS on entry | M [IQR] | M [IQR] | M [IQR] |

Table 5. Comparison of change in primary outcome measures Study 2

| | **Group A** | **Group B** | **Group C** | **DIM** | **2p** |
|---|---|---|---|---|---|
| PAS | M [IQR] | M [IQR] | M [IQR] | MWU | |
| DSRS | M [IQR] | M [IQR] | M [IQR] | MWU | |
| FOIS | M [IQR] | M [IQR] | M [IQR] | MWU | |

Table 6. Adverse events and Withdrawal Study 2

| | **Group A (n=16)** | **Group B (n=16)** | **Sham (n=16)** |
|---|---|---|---|
| CI during admission | M [IQR] | M [IQR] | M [IQR] |
| In hospital mortality | N (%) | N (%) | N (%) |
| SAE | N (%) | N (%) | N (%) |
| Death | N (%) | N (%) | N (%) |
| Withdrawals | N (%) | N (%) | N (%) |