Protocol for TMS-Neurofeedback Stroke Experiment

NCT Number (not yet assigned)

Date: 18/10/23

1. Overview

Upper limb weakness following a stroke affects most survivors and is a key factor in preventing them from returning to independent activities of daily living. Most of the current state-of-the art approaches to rehabilitation require that the patient can generate some activity in the paretic limb, which is not possible for many patients in the early period following stroke, nor for some patients even in the chronic period. This delays and prevents their participation in physical therapies. Approaches that enable more patients to engage with movement therapies at an earlier timepoint during the 'sensitive period' following stroke are greatly needed.

Despite having no functional movement in the paretic limb, most stroke patients exhibit Motor Evoked Potentials (MEPs) when stimulated over the damaged motor areas of the brain using Transcranial Magnetic Stimulation (TMS). This indicates intact pathways from the brain to the muscles and has been shown to predict better subsequent functional recovery (*Stinear et al, 2012; Byblow et al. 2015*). In the early days following stroke, the excitability of neuronal pathways from the brain to the muscles is substantially reduced. This most likely reflects the demyelination of axons, leading to conduction failure. Within the first 12 weeks, a degree of spontaneous proportional recovery of motor function typically occurs, up to 70% of the individual's maximum possible improvement. Interestingly, this time course of recovery coincides with the resolution of corticomotor excitability (MEP amplitudes), which also resolves to 70% of normal levels within the same 12 week period (Byblow et al. 2015; Cicinelli et al., 2003; Thickbroom, Byrnes, Archer, & Mastaglia, 2004). The interconnectedness of the functional recovery process and resolution of corticomotor excitability provides some insight into the neurobiology of spontaneous motor recovery and raises the intriguing possibility that perhaps interventions directly targeting the neural mechanisms of corticomotor excitability in this sensitive period would causally impact upon and accelerate recovery.

In the absence of being able to generate movement in the paretic limb, motor imagery has been suggested to activate many of the same brain-muscle circuits as actual movement. However, as imagery is a hidden mental process, it is impossible for individuals to gauge what impact this is having upon their neural activity, to learn how to best exploit this mechanism to augment stroke recovery.

This research project is an investigation into the mechanisms and efficacy of using a novel brain-computer interface (BCI) (eg. Ruddy et al., 2018) based upon muscle responses to TMS to provide feedback (visual and auditory) to stroke survivors while they perform motor imagery.
Using this approach, magnetic pulses will be applied to the scalp over the location on the motor cortex that controls the arm and hand, via TMS. This evokes a twitch in the stroke-affected muscles (the MEP), which is recorded using electromyography (EMG). The size of MEPs are displayed to the patient in real-time, with rewarding visual and auditory feedback incorporated in a game-like display. The patient is instructed to learn how to make MEPs bigger using motor imagery, guided by the feedback from the brain-computer interface.

We hypothesise that training using TMS-neurofeedback will lead to increases in MEP amplitudes, compared to a control group receiving pseudofeedback. We will investigate whether these changes in MEP amplitudes correlate with enhanced or faster than usual functional improvement and explore the underlying structural and neurochemical brain mechanisms of recovery.

2. Patient characteristics and exclusion criteria
20 patients (10 in TMS NF group, 10 in Pseudo-feedback group). Sub-acute: 2-26 weeks post stroke. Would prefer 2-12 weeks if feasible as there is a critical period in first 12 wks. First stroke (no previous TIAs). Single Hemisphere lesion. Low/No residual movement in lower arm and hand. MEP positive (in response to TMS). No or negligible OCS broken hearts cancellation test score (visual neglect) 6. No or almost no cognitive impairment (Pass or near pass MMSE and MOCA) 7. Passes TMS-Safety Questionnaire (no contraindications to TMS)

3. Recruitment Procedure
Patients informed about the study directly via consultant Prof. Harbison and his team and provided with information sheets detailing how to contact the researchers if interested.

4. Procedures with Patients

4.1 Informed Consent and Providing Information
The patient should be asked to read through the information sheet prior to coming to the first day of the experiment. However, when they arrive for the first session, provide them again with the information sheets and go through them page by page reading and explaining everything to them, answering any questions. When the patient has understood everything, read through the consent form with them, answering any questions, and if they consent to participate ask them to sign their name. If they are unable to sign the consent form, their next of kin can provide consent by proxy. At this stage they will be assigned an

anonymous code which will be used to identify their data and assigned to Group A or Group B using a computer algorithm.

4.2 Familiarisation Session

This can be conducted on the same day as the signing of the informed consent forms. The patient should be given the opportunity to experience the feeling of TMS prior to commencing with the experimental sessions. The participant will have a fabric cap placed on their head, with a grid drawn on it, indicating the midpoint (vertex) of the head and locations relative to it. The TMS coil will be positioned on the head over the motor cortex on the healthy hemisphere (5cm lateral and 1cm anterior from the vertex), and a weak magnetic pulse applied. The patient will be asked whether they can feel anything. The intensity of the pulses will then be turned up gradually, asking the participant with each increment if the pulse still feels comfortable. When the stimulation intensity is sufficient to evoke a response (MEP) in the index finger muscle of at least 50uV, 5 such pulses will be applied with intervals between 6-8 seconds, to establish the average MEP amplitude at this scalp location. The coil position will then be moved left and right, forwards, and backwards at 1cm increments relative to the starting position, until the position with the largest and most reliable MEPs is located (the motor 'hotspot'). On the hotspot, the experimenter will next establish the patients *resting motor threshold* (RMT). That is, the lowest stimulation intensity that produces MEPs greater than 50uV on 5/10 trials.

When the hotspot and RMT have been established on the healthy hemisphere, this procedure will be repeated on the stroke affected hemisphere, guided by the knowledge of motor cortex positioning on the healthy hemisphere. The RMT is typically much higher on the stroke affected hemisphere, so a higher intensity of stimulation will be required to evoke responses. The RMT for both hemispheres will be noted for future reference, and the position of the hotspot on both hemispheres will be noted on the fabric cap. This is to assist positioning of the TMS coil for all subsequent sessions and negate the need for extensive mapping of the scalp on each new day of testing.

The patient will then be familiarised with the mental imagery requirements of the protocol. They will then be asked to imagine the *feeling* of performing movements with the stroke affected limb and told that this type of imagery will be required to influence the amplitude of their MEPs during the training sessions.

At this stage, if the patient has no MEPs in response to TMS, unfortunately they will not be able to participate further in the study (or, if willing, try again in a week to see have MEPs recovered).

4.3 Baseline Functional and Cognitive Assessments

Prior to commencing the first TMS NF training session, the patient will have their upper limb function assessed by a member of the team (not the same member who will perform the TMS, for blinding reasons). They will perform the Fugl-Meyer task assessing the quality of a range of upper limb movements, and the Action Research Test (keeping a long break between these two tests to avoid fatigue or coming back on a separate day to perform one of the two functional tests). They will complete standard questionnaires assessing cognitive function and mood/depression (the Oxford Cognitive Screen, and the Hospital Affective Disorders Scale). They will also complete the National Institute of Health Stroke severity scale (NIHSS), Motor imagery ability questionnaire, a sleep questionnaire and measure muscle circumference in forearm and bicep of both arms.

If all tests above conducted together, estimated time is approx. 1 hour 30 minutes, so allow 2 hours for this session with comfort break for patient.

4.4 MRI scanning

Following the familiarisation session and baseline functional and cognitive assessments, the patients will be invited to undergo a series of MRI brain scans in the Centre for Advanced Medical Imaging (CAMI), on the site of St. James Hospital. Total scanning time will be 1 hour per participant, which will comprise of the following types of scans:

1. High resolution T1 anatomical scan (grey matter)
2.Diffusion weighted imaging (DWI) scan (white matter)

4.5 TMS NF training sessions 1-4

4.5.1 Training sessions overview

The TMS sessions should be spaced at maximum of 72 hours apart, ideally session 1-4 should occur all within the same 7-day period.
When the patient arrives for each training session, they will sit in a comfortable chair or bed with arms supported on foam pillows and have their muscles prepared with exfoliant skin preparation paste and an alcohol wipe. Electrodes will be placed over the target muscles (hand and arm muscles).
The research team will place the TMS coil over the hotspot that was located during the familiarisation session. On this location (separately for healthy and stroke affected hemisphere), we will measure the patients RMT.

4.5.2 TMS neurofeedback block

The patient will be positioned in front of a computer monitor and will receive a block of 20 neurofeedback trials. Each trial contains just one TMS pulse, so in total they will receive 20 TMS pulses (at an intensity that is 120% of the RMT) with an interval of 6-8 seconds between pulses. Each TMS pulse will be followed immediately by feedback on screen in the form of a vertical bar. The height of the bar indicates the amplitude of the MEP recorded in the muscle, and this is shown relative to a horizontal white line that indicates their baseline MEP amplitude. If the current MEP on a given trial is larger than baseline, the trial is deemed 'successful'. The vertical bar will be green, with a green tick on screen beside it, and a positive sound-byte will be played. If the MEP amplitude is below baseline, the trial is unsuccessful; The bar will be red, with a red cross, and a negative sound-byte will be played. Patients will be told that their goal is to accrue as many successful trials as possible, and that the height of the bar can be influenced by imagining movements using the stroke affected limb (specifically, the stroke affected finger muscles).

This block of neurofeedback takes approximately 6 minutes, and is repeated three times during the course of the training session, with rest breaks for the patient between blocks.

At the end of the training session, we will record MEPs from 20 TMS pulses while the patient is at rest, viewing a fixation cross (for pre-post measurement of resting corticospinal excitability).

4.5.4 Pseudofeedback group

The control (pseudofeedback) group (n=10) will undergo identical procedures to the experimental group, but with the on-screen feedback bar height in the game changed such that it does not represent MEP amplitude, but instead shows a bar of fixed height, with a predictable reward schedule. This prevents learning how to control the bar in the game, and thus allows us to investigate whether patients using the feedback to learn to up-regulate excitability demonstrate better functional upper limb outcomes compared to those who did not. The application of TMS is identical for both groups- the only thing altered is their visual feedback.

4.6 Follow up/Top-up sessions

Following the initial 4-day training period, patients will return for follow-up training sessions 2 weeks, 6 weeks, 12 and 26 weeks later. RMT will be recorded at each follow-up session to monitor changes in corticospinal excitability. Three blocks of TMS NF will be completed, and a sub-set of the functional and cognitive measures will be collected (see case report form for list of tests to be conducted on each follow up.

4.7 Post-Training Functional/Cognitive/MRI assessments

At the end of the final follow-up session 6 months following initial training, patients will have the same full assessments of upper limb function and cognition performed, as were completed prior to the first session. The same set of MRI scans will also be repeated in CAMI.

5.0 Completion of study with participant

Upon completion of the final session of the experiment, the patient should be provided with the debriefing leaflet, which will be discussed with them. They will be informed that from now on, their name and contact details will be deleted from our database and the data we have recorded from them will be anonymised. At this point, the experimenter should ensure that the patients identifiable information is deleted from the spreadsheet linking their anonymous code to their name and contact details.