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Transcranial magnetic stimulation as a treatment for functional (psychogenic) upper limb weakness

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ABSTRACT

Objective: There has been a recent resurgence of interest in physical treatments for functional motor disorders (FMD) including Transcranial Magnetic Stimulation (TMS). This pilot study aimed to test the effectiveness of a single session of motor cortex TMS as a treatment for functional upper limb weakness.
Methods: Ten subjects with a diagnosis of functional upper limb weakness were randomised to immediate ($n = 7$) or delayed (3 months) ($n = 3$) TMS treatment. Median age was 35 (range 23–52) and median symptom duration was 2.3 years (range 5 months – 20 years). 46–70 single pulses were applied to the motor cortex at 120–150% motor threshold. We used a verbal protocol designed to standardized the effects of suggestion. Primary outcome measures were self-reported symptom severity, grip strength and tapping frequency immediately after treatment, and symptom severity and disability (SF-12 and Modified Rankin Scale (MRS)) after 3 months.
Results: There was a small significant reduction in symptom severity immediately after treatment, but no improvement in grip strength or tapping frequency and no change in symptom severity, SF-12 or MRS 3 months after treatment. Small numbers precluded comparison of immediate treatment with delayed treatment. Four of eight subjects responding to three-month follow-up reported late-onset adverse effects.
Conclusion: This pilot study suggests limited benefits for TMS as a one-off non-neuromodulatory treatment for stable chronic outpatients. TMS may still have a role alongside more intensive multidisciplinary therapy input, or in patients with severe deficits where the possibility of normal movement can be hard to demonstrate.
Trial registration: NCT02102906

1. Introduction

There is a rich history of electrical treatments for functional motor disorders (FMD), but such techniques fell out of favour after the First World War [1]. The development of Transcranial Magnetic Stimulation (TMS) has led to resurgence of interest with recent studies suggesting effectiveness of motor cortex stimulation in treatment of FMD.

A systematic review in 2014 identified ten studies of TMS for the treatment of FMD, treating 95 patients in total (78 with weakness) [2]. All but one study reported improvement after treatment [3,4], including in symptoms of long duration. For instance, in a study of 24 patients with a median symptom duration of 2.8 years, 75% had an immediate improvement in symptoms with benefit sustained beyond a year [5]. Another small pilot study found no symptomatic treatment effect in 11 patients receiving repetitive TMS, although there was some transient increase in muscle strength [6].

Where TMS has shown beneficial effects in FMD, mechanisms are unclear, and heterogeneity of TMS protocols between studies (ranging from a single session of 30 pulses [7] to 4000 pulses of rTMS daily for 4–12 weeks [3]) makes it difficult to test hypotheses. It has been suggested that TMS might cause neuromodulation, although good effects have been reported in studies using TMS regimes which would not be expected to cause lasting neuronal change. Others have suggested that placebo factors may be important.

One compelling idea is that supraliminal motor cortex TMS can demonstrate movement in an apparently paralysed limb, demonstrating to the patient that a) pathways from brain to limb are intact and b) potential for movement and therefore recovery exists [2]. This theory can be understood in the context of a paradigm described by Edwards et al., in which beliefs about movement exert a top-down influence on sensorimotor processing to produce symptoms of Functional Neurological Disorder [8].

The TMS protocols reported in other studies are often complex, involving multiple treatment sessions, or report retrospectively on TMS used primarily for diagnostic purposes. In particular all of those studies

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applied TMS at the same time as other potentially therapeutic interventions including explaining the diagnosis, or providing physical rehabilitation or psychological therapy. The largest study treated patients with a mean duration of symptoms 5 days with many paediatric patients [4]. The second largest study gave rehabilitation and explanation at the same time [5].

In contrast, this study aimed test the effectiveness of a simple TMS protocol without additional treatments alongside. This centre has previously reported positive experiences of using therapeutic sedation and demonstration of the Hoover's sign to patients in order to demonstrate normal movement in functionally dystonic or weak limbs [9,10], and ultimately it was hoped that TMS treatment, via similar mechanism, might be a useful addition to the repertoire of treatments offered by this service.

The intention of this pilot study, therefore, was to test the effectiveness of a single session of supraliminal TMS, as a means of demonstrating movement, as a treatment for functional upper limb weakness.

2. Methods

Subjects were recruited from routine consultant neurology (JS) and neuropsychiatry (AC) clinics. Subjects met inclusion criteria who were between age 18 and 75 and had a functional upper limb weakness as part of functional neurological symptom disorder according to DSM-5 criteria on the basis of positive clinical features. Diagnosis was made by a Consultant Neurologist (JS, eight cases) and a Consultant Neuropsychiatrist (AC, two cases) both with expertise in Functional Disorders.

Upper limb weakness was specified as the target symptom because the intention was to effect movement of a functionally weak limb, and the arm and hand areas of the motor cortex are more consistently accessible to superficial stimulation than the leg area which can be more difficult to stimulate because of its deeper central location.

Subjects were excluded who: did not speak English, had dementia or learning disability, alcohol dependence (as assessed by AUDIT screening questionnaire [11]), psychosis, suicidal ideation or severe personality disorder, cardiac pacemaker or other metal implant [12,13], a history at any time since birth of epileptic seizure. Factitious disorder was also an exclusion criterion; although it is impossible to completely exclude factitious disorder, participants were excluded where there was suspicion of factitious disorder or malingering, such as evidence of an extreme discrepancy between observed and reported function or clear reasons for malingering such as ongoing litigation.

The study received NHS Research Ethics Committee approval, and the trial was registered at www.clinicaltrials.gov (NCT02102906).

Participants signed a consent form after discussion with a researcher and provision of written information about the study, including explanation of the possible important role of placebo factors. Hospital Anxiety and Depression Scale (HADS) [14], Alcohol Use Identification Test (AUDIT) [11] and TMS safety questionnaires [12,13] were completed prior to randomisation. Subjects who consented to participate and met inclusion criteria were allocated a study number. A consultant not involved with the study used a computerised random number generator (http://www.randomization.com) to generate a randomised list of condition (immediate or delay) against study number, and this consultant was contacted by email to obtain the condition for each participant after consent was obtained.

Baseline self-reported symptom severity, disability, illness and treatment beliefs were assessed by Short Form 12 (SF-12) [15], Modified Rankin Scale (MRS) [16] and a study-specific pre-TMS questionnaire immediately after randomisation in those randomised to delay, who then received usual care for 3 months before attending for treatment. These measures were assessed on the day of treatment for all participants including those randomised to delay.

Participants attended the University of Edinburgh Psychology Department on a single occasion between December 2014 and September 2015. As part of a separate study, each participant first completed a 30-min set of neuropsychological tests of verbal response latencies to visual stimuli on a computer screen. After completing these tests, a standardized explanation about TMS was given to participants (Table 1). Primary outcome measures of disability (SF-12 and MRS) and self-reported symptom severity (5-point Likert Scale) were taken immediately before treatment. Secondary outcome measures of impairment in the affected upper limb were also taken immediately before treatment: hand grip strength in kg (tested using a hand dynamometer – best of three) and tapping frequency (maximum taps of the spacebar within ten seconds - best of three). Outcome measures were assessed by the doctor performing TMS, who was therefore not blinded to group allocation or treatment effect.

A Magstim Rapid 2 magnetic stimulator was used with a round coil and foot switch.

Table 1
Treatment protocol.

Protocol for explanation and procedure of TMS treatment of functional movement disorder used in this study
• Explanation that TMS is a standard diagnostic procedure that has been around for over 20 years and we are not using unusual strengths. There is no evidence that TMS causes any problems other than to people with epilepsy
• Warning about electrical sensation on head
• The procedure is for treatment not diagnosis
• TMS is being given to explore whether producing movements through the machine may allow improvement in symptoms by
○ Normalization of the brain pathways that have been disrupted in functional disorder.
○ Giving the brain some new 'feedback' from the affected limb that could help restore function (biofeedback)
○ A form of suggestion or placebo
• Movement may occur more after procedure as much as during it
• An understanding that this is not going to be a repeated procedure
• For patients with complete paralysis –
○ Consent for sensory stimulation including nailbed pressure
○ Discussion of how the patient would handle sudden recovery with family and friends (i.e. would they worry that others thought they had been feigning if they suddenly improved? If so anticipate strategies to compensate. e.g. "Family and doctors know you are not feigning", "If others happen to think this then that is a small price to pay for regained function").
Procedure
• Patient seated in comfortable chair
• Relative or friend may be present if they wish
• Plenty of encouragement throughout. Use of humour, personal information from patient as appropriate
• Find threshold using single coil 90mm on contralateral motor cortex to produce wrist or finger movement. Motor threshold should be taken as the intensity at which 3/5 stimulations produce visible movement.
• If possible, stimulate leg movement using the round coil if the patient's leg is affected
• Apply at 125% of threshold, or higher if tolerated, to induce elbow/wrist/finger movements
• Aim for at least 50 stimulations over a 30 minute period, carrying out 4-5 stimulations at a time 3-4 seconds apart
• Examples of comments to make during procedure
○ "Let's see if we can get those automatic normal movements going again."
○ "That was a good movement - let's do that again."
○ "How does it feel to see that movement?" – "Is it a good feeling?"
○ "Don't fight the strange feeling of your arm/leg moving again."
• After a series of five stimulations, carry out power testing as a form of 'physio' to capitalize on any improvements during the procedure. Example movements include
○ Elbow flexion against resistance
○ Wrist flexion against resistance
○ Finger flexion against resistance
○ Knee flexion against resistance
○ Ankle plantar flexion against resistance
• In patients with dense sensory loss (unusual) use sensory stimuli (which all should be consented prior to the procedure) include
○ Nail bed or sternal pressure
○ Induction of plantar or deep tendon reflexes
• Continue for no longer than 30 minutes but shorter if the patient prefers to stop (check the patient is happy to carry on after each group of 4-5 stimuli)
• If there is a dramatic improvement continue to reinforce movements after procedure.