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

Laura McWhirter [a,b,*], Lea Ludwig [c], Alan Carson [b,d], Robert D. McIntosh [e], Jon Stone [b]

[a] Royal Edinburgh Hospital, Edinburgh, United Kingdom
[b] Department of Clinical Neurosciences, Western General Hospital, Edinburgh, United Kingdom
[c] University of Hamburg, Germany
[d] Department of Rehabilitation Medicine, Astley Ainslie Hospital, Edinburgh, United Kingdom
[e] Psychology, University of Edinburgh, United Kingdom

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.
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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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* Corresponding author.
E-mail address: lauramcw@doctors.org.uk (L. McWhirter).

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.

Single pulses were administered at no greater than 0.3 hertz. Motor threshold was estimated, pragmatically, as the strength of stimulation at which three out of five stimulations created a visible movement in the limb. The stimulation intensity was then gradually increased to 120–150% of motor threshold, as tolerated and guided by the participant, and a further 46–70 single pulses (variation reflecting patient preference) were administered in sets of 4–5 pulses 3–4 s apart, producing palpable and usually visible muscle jerks of the hand and/or arm.

The verbal protocol and procedure is described in Table 1. This verbal protocol was used in order to standardise the effects of suggestion, and was similar to that used in a study of therapeutic sedation for functional dystonia [9].

The primary outcome measure of self-reported symptom severity was assessed immediately after treatment as part of a set of study-specific questionnaires which also included questions assessing participant perception of treatment effectiveness ('How effective was TMS treatment for your symptoms?'), tolerability of treatment ('How painful or uncomfortable was TMS treatment'), and a checklist of adverse effects with space for free-text responses.

Primary outcome measures of SF-12, MRS, and self-reported symptom severity were repeated 3 months after treatment together with a study-specific questionnaires including questions about treatment effectiveness and adverse effects.

Statistical analysis was performed using SPSS v21. Shapiro-Wilk tests were performed to check data for normality; where normally distributed, paired samples t-tests were used to compare measures before and after treatment, and where data at one or both time-points was not normally distributed the Willcoxon Sign Rank test was used.

3. Results

Thirteen patients were recruited. One did not meet inclusion criteria, eight were randomised to immediate treatment and four to three-month delay; two withdrew before treatment and ten attended for treatment (seven immediately and three after delay). These 10 patients had the following characteristics: 6 female, 4 male; median age 35 years (range 23–52); 9 right handed, 1 left handed; median duration of symptoms 2.3 years (range 5 months to 20 years); 6 left sided weakness, 4 right sided weakness; Mean HADS score 14.1 (range 2–29, SD 7.8) SF-12 scores were similar before (mean ± SD:PCS 32.5±0.2, MCS 35.4± 11.1) and after delay (35.1±10.3, MCS 43.3±11.0), and MRS scores were similar before (2 ± 1) and after delay (2 ± 1). Clinical characteristics, comorbidities, prior investigations, and response of subjective symptom severity to treatment are presented in Table 2. The trial was terminated prematurely (the original intention being to recruit 40 participants) as a result of difficulties recruiting patients – the target condition of unilateral upper limb weakness being less frequent in clinics than was projected – and because the treatment as given did not seem effective. Small numbers precluded analysis of immediate vs delayed treatment.

Prior to treatment, eight participants agreed or strongly agreed with the diagnosis of functional disorder; two strongly disagreed. Two participants believed TMS was 'likely' to help their weakness and eight were 'uncertain'. No participants reported discomfort during the procedure. Two reported mild headache, three mild tingling and one mild difficulty concentrating immediately after TMS.

Overall there was a significant reduction in self-reported symptom severity immediately after treatment (Willcoxon Signed Rank test $p = 0.05$). Three participants reported a reduction in severity from 'severe weakness' to 'moderate weakness', and one participant from 'moderate weakness' to 'mild weakness'. The remaining six participants reported no change in symptoms severity after treatment. Improvements in self-reported symptom severity were not reflected by objective measures, and there was no significant difference in grip strength ($p = 0.28$) or tapping frequency (Willcoxon Signed Rank test $p =$

0.89) after treatment. No patient reported delayed improvement after the treatment which had reversed by the time of follow up.

Eight subjects (two after delayed treatment) returned three-month follow-up questionnaires. At 3 months, there were no significant differences compared with before treatment in the primary outcome measures of self-reported symptom severity ($p = 1$), SF-12 PCS score ($p = 0.17$), SF12 MCS score ($p = 0.91$)($p =$) or MRS score (Willcoxon Signed Rank test $p = 1$) (Table 3).

One participant, with functional hemianaesthesia, reported no improvement in weakness but 15-min episodes of restored sensation every 10 days during the 3 months of follow-up, and another reported improvement in handwriting.

However, four of the eight participants to return follow-up questionnaires reported adverse effects. One reported a severe headache arising on the day of treatment and persisting for 24 h, one "a thumping sore head for a few weeks", another increased difficulty writing and opening things using the symptomatic hand for 2 days. Another reported a severe two-week long episode of dissociative regression: "forgetting simple things like what things tasted like, what people looked like and even how to do banking".

4. Discussion

This pilot study of TMS as a treatment for FMD used a reproducible, pragmatic TMS protocol, and a pre-defined verbal protocol designed to standardise the effects of suggestion. All participants found treatment tolerable and there was a small immediate improvement in weakness in around half the patients, but the improvements were not judged clinically significant nor were they sustained at 3 months.

The largely negative results of this small study differ from the striking positive results previously reported elsewhere. There are a number of possible reasons for this.

Most of our patients had already explored other treatment options and on the whole represent a group with chronic, stable, treatment-resistant symptoms, which may in part account for the poor response to treatment. By comparison one of the most positive studies of TMS used it in patients presenting acutely, many of whom may have improved anyway and in a way that would have been difficult to disentangle from the potentially positive effects of explanation and meeting a clinician interested in treating their disorder [4].

The second-largest previous study used TMS in combination with multidisciplinary rehabilitation, again casting doubt on its specificity [5]. In contrast, the TMS in this study was given in a single session, at a location and date remote from clinic follow-up, and no additional rehabilitative input was provided; we separated out the TMS from the other treatments and found that TMS alone was not effective.

It may be that similar treatment given in the context of more intensive multidisciplinary therapy input might have had better and more synergistic effects. Ongoing therapy alongside TMS may, among other things, encourage ongoing confidence in the diagnosis of functional disorder (a prognostic factor) and by this mechanism increase the likelihood of sustained improvement after TMS; we were somewhat surprised to note that two of our participants 'strongly disagreed' with the diagnosis of functional disorder and also note that only two believed that TMS was 'likely to help' their weakness with the remaining eight 'uncertain', suggesting that confidence in the diagnosis had lessened since last clinic follow-up.

It could be argued that transparent explanation of possible placebo effects associated with TMS might have reduced the strength of these effects. However, studies of open-label placebos have demonstrated positive placebo effects even where patients are aware that they were taking an inert substance [17,18]. We do not consider TMS to be an 'inert' treatment, only that placebo factors may contribute to treatment effects.

Also of note, four of the eight participants in this study to return follow-up questionnaires reported significant side effects with delayed

Table 2
Clinical characteristics and self-reported symptom severity before and after TMS.
All patients were diagnosed and received detailed explanation and support from a specialist in functional disorders (neurologist (JS) or neuropsychiatrist (AC)); HADS, hospital anxiety and depression scale; HADS-A, anxiety subscale; HADS-D, depression subscale; SF-12, short-form 12 health survey; FDS, functional disorders specialist (consultant neurologist or neuropsychiatrist); severity scores 1–5 (1 'no weakness at all', 2 'mild weakness', 3 'moderate weakness', 4 'severe weakness', 5 'very severe weakness'); L = Left; R = Right.

Age	Sex	Handedness	Functional symptoms	Comorbidities	Duration of arm weakness	Relevant Medication	Previous investigations	Additional Previous treatment	HADS score, (HADS-A, HADS-D)	Day of treatment SF12 PCS, MCS / Modified Rankin Score	Symptom severity pre-TMS 1-5	Symptom severity immediately post-TMS 1-5	Symptom severity 3 months post-TMS 1-5	SF12 / Modified Rankin Score 3 months post-TMS
48	M	L	L arm / leg weakness, hemi-anaesthesia	Splenectomy, hypertension	20 years	Sodium valproate, Gabapentin, Co-codamol, Amitriptyline, Trazodone,	MRI brain and whole spine -normal	Outpatient specialist physiotherapy	10 (5, 5)	23, 53 / 3	4	3	4	18, 54 / 4
39	M	R	L arm weakness, R leg weakness, intermittent dysarthria		5 years		MRI brain - nonspecific white matter hyperintensities. MRI whole spine -normal	Outpatient specialist physiotherapy	24 (9,11)	51, 25 / 3	4	4	4	30, 27 / 4
41	F	R	L arm and leg weakness	Right trigeminal neuralgia	5 months	Gabapentin, Carbamazepine, Dihydrocodeine, Paracetamol	MRI brain - normal	Inpatient specialist physiotherapy	19 (9,10)	31, 40 / 3	2	2	Did not return follow-up questionnaires.	Did not return follow-up questionnaires.
41	F	R	L arm / hand weakness	None	2.5 years	none	X-ray and MRI wrist (reported normal)	Physiotherapy	11 (5,6)	49, 54 / 1	4	4	4	37, 34 / 0
23	F	R	R arm / leg weakness	None	15 months	none	MRI brain and cervical spine both normal		20 (13,7)	41, 30 / 4	4	4	Did not return follow-up questionnaires.	Did not return follow-up questionnaires.
25	F	R	R arm/ leg weakness, dissociative seizures,	Migraine	12 months	Topiramate, Tramadol, Dihydrocodeine, Cyclizine	MRI brain and whole spine normal	Cognitive behavioural therapy for dissociative seizures	14 (11,3)	31, 46 / 3	3	2	3	26, 49 / 2
31	F	R	R arm / leg weakness	Irritable bowel syndrome, mild depression.	1 year 9 months	Mirtazapine	MRI brain and lumbar spine - normal		13 (7,6)	36, 56 / 1	2	2	2	53, 44 / 1
53	M	R	L arm / leg weakness	Obstructive sleep apnoea, restless leg syndrome	6 years	Ropinorole, Rabeprazole, Tramadol, Diazepam, Sertraline, Trazodone, plus,	MRI brain -nonspecific white matter hyperintensities. MRI cervical spine - no relevant changes		2 (1,1)	23, 54 / 4	4	3	4	15, 55 / 4
24	F	R	L arm / leg weakness,l visual impairment, dissociative seizures	Bipolar affective disorder (euthymic at time of participation), slow-transit constipation, asthma.	6 years	Lithium, Quetiapine, Cetirizine, Docusate, Linaclotide, Metaclopramide, Mirabegron, Monteleukast, Omeprazole, Peppermint oil, Procyclidine.	MRI brain and spine - normal		Not completed	25, 39 / 4	4	3	5	19, 43 / 4
24	M	R	R arm / hand weakness	None	2 years	none	MRI shoulder and brachial plexus- no relevant abnormalities.Neurophysiology normal.	Physiotherapy.	9 (5,4)	42, 35 / 2	3	3	2	36, 59 / 2

Table 3
Outcome measures pre- and post-TMS treatment. Mean [range, SD], Median (range).

	Day of treatment (n = 10)		3 months after treatment (n = 8)[1]
	Pre-treatment	Immediately post-treatment	
'How severe is your weakness at the moment?' (1 = 'no weakness' – 5 = 'very severe weakness')	3.4 [2-5, 0.8]	3.0 [2-4, 0.8]	3.5 [2-5, 0.8]
Grip strength on symptomatic side, kg, before treatment / immediately after treatment	10.9 [0-25, 8.1]	13.8 [0-30, 9]	
Maximum finger taps in 10 seconds on symptomatic side, before treatment / immediately after treatment	42.5 (0-59)	41 (0-53)	
Modified Rankin Scale	3 (1-4)		3 (0-4)
SF-12 - PCS	34.9 [23-51, 11.4]		29.2 [18-53, 12.8]
SF12 - MCS	45.3 [25-56, 11.2]		44.8 [27-55,10.5]

onset. Adverse effects of this nature have not previously been reported in studies of TMS for FMD. There are several possible mechanisms for the reported late-onset adverse effects. It is possible that the physical and unfamiliar nature of the sensations associated with TMS may bring about mild anxiety and a temporarily heightened awareness of bodily sensations. Post treatment anxiety and hyperarousal may have contributed to the period of dissociation reported by one participant after treatment. Although mild headache after TMS is normal, the two patients who reported prolonged headache perhaps demonstrate increased vulnerability to abnormal pain responses in patients with functional disorders. As medical interventions are common trigger events for functional disorders in the first place, the possibility of this intervention having negative effects on symptoms, or triggering new symptoms, may be an important consideration.

In summary, the findings of this small study of a single session of supraliminal TMS in stable chronic outpatients who have already explored other treatment options are not encouraging and suggest that some of the reported treatment effects from other studies may be the result of interactional processes between treating health professional and patient. However, TMS may have a helpful role as a part of a multidisciplinary rehabilitation programme, and in particular with patients who have severe deficits such as weakness, blindness or anaesthesia where reversibility of the symptom and therefore potential for improvement is hard to demonstrate in other ways.

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