REVIEW

A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms

Thomas A Pollak,[1] Timothy R Nicholson,[1] Mark J Edwards,[2] Anthony S David[1]

[1]Section of Cognitive Neuropsychiatry, Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, UK
[2]Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, University College London, London, UK

Correspondence to
Dr Thomas A Pollak, Section of Cognitive Neuropsychiatry, Department of Psychosis Studies, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK; thomas.pollak@kcl.ac.uk

ABSTRACT

Functional (conversion) neurological symptoms (FNS) are commonly encountered in neurological and psychiatric clinical settings and represent a considerable burden on healthcare systems. There is a conspicuous paucity of evidence-based treatments for FNS. Transcranial magnetic stimulation (TMS) offers a safe, non-invasive method of probing changes in cortical excitability and/or connectivity. It has already had some success in demonstrating abnormalities of cortical excitability in patients with FNS, particularly when the functional symptom in question relates to movement. We reviewed the literature for studies in which TMS has been used in the treatment of FNS. All patients in the identified studies had motor symptoms (either weakness or movement disorder). There was considerable heterogeneity in terms of study quality, population sampled, study design, TMS parameters and outcome measures. No studies were placebo controlled. Despite the majority of studies claiming success for the technique, there is insufficient good quality evidence to establish TMS as an effective treatment modality for FNS. We outline the methodological considerations that should be taken into account in future studies of the efficacy of TMS in treating FNS and discuss mechanisms by which TMS, if efficacious, may exert a therapeutic effect, including: (a) via genuine neuromodulation, (b) via non-specific placebo effects and (c) by demonstrating, through its immediate effects on the motor system (eg, movement in a 'paretic' limb), that symptom improvement is possible, thus directly changing higher level beliefs that may be responsible for the maintenance of the disorder.

INTRODUCTION

'Functional neurological symptoms' (FNS) refers to the presence of neurological symptoms and signs that are incongruent with, or not fully explained by, organic neurological disease. FNS are common. A multi-centre prospective cohort study examined 3781 new neurology outpatient referrals and found that 30% had symptoms that were not at all or only somewhat explained by neurological disease.[1] In all, 16% of all new referrals were categorised as having a 'functional' or 'psychological' diagnosis.[2] Previously known as hysteria, such symptoms are commonly labelled as conversion, psychogenic, non-organic, dissociative or functional,[3] each title suggesting a varying degree of belief in the aetiological role of psychological factors. In the current diagnostic system these symptoms are recognised as 'conversion disorder' and *require* the presence of a psychological stressor. This is controversial and the criterion may be dropped for DSM-V.[4]

The psychological mechanism is assumed to be subconscious and therefore it is thought to differ from consciously generated ('feigned' or 'malingered') symptoms, although the demonstration of this is often practically unworkable in normal clinical practice.[3] Neuroimaging and neurophysiological studies largely support this differentiation and have started to provide some insights into the possible aetiological mechanisms of FNS (at least of the motor subtype) that include abnormalities in frontal, parietal and limbic influence on the motor system.[5–7] Some have argued that they have clinical, psychological and neurobiological similarities to hypnotically induced neurological symptoms.[8 9]

There is a conspicuous paucity of evidence-based treatments for FNS. Many centres place emphasis on cognitive behavioural therapy (CBT) and physiotherapy, which may both broadly be seen as helping the individual to 'unlearn' maladaptive or pathological somatic states or tendencies. There is some preliminary evidence for the role of CBT[10] and physiotherapy[11] in particular kinds of FNS but other psychological treatments have little proven efficacy.[12]

Transcranial magnetic stimulation (TMS) offers a safe, non-invasive method of probing changes in cortical excitability and/or connectivity. It has already had some success in demonstrating abnormalities of cortical excitability in patients with FNS, particularly when the functional symptom in question relates to movement.[13–15] Repetitive TMS (rTMS) can induce lasting changes in cortical excitability which is similar to long-term potentiation and long-term depression effects seen after direct neuronal stimulation in experimental animals.[13] rTMS has been widely used as a technique to probe brain plasticity in humans both in an attempt to understand the pathophysiology of some neurological diseases and as a potential therapeutic tool in a number of neurological and neuropsychiatric conditions.[13 16]

It is against this background that TMS has been explored as a possible treatment for FNS. Here we critically review the literature to date on this topic and provide suggestions for future exploration of this therapeutic tool.

Neuropsychiatry

METHODS
Search protocol
The current study aimed to review all published reports of the use of TMS in the treatment of FNS.

A literature search was performed using the following databases: MEDLINE, PubMed, Embase, PsycINFO, Web of Knowledge and Scopus all till November 2011.

Database controlled vocabulary headings for conversion disorder and hysteria were used as well as the following text terms that can be used to describe the condition: conversion, non-organic, psychosomatic, psychogenic, somati*ation, somato-form, unexplained, and dissoc*. These were combined with the terms 'TMS', 'rTMS' or 'transcranial magnetic stimulation'. Non-English publications were included.

Inclusion criteria
Studies were included if they met the following criteria:
A. Patients' symptoms were described as medically unexplained, non-organic, psychogenic, hysterical, conversion or functional.
B. Symptoms described were motor or sensory. Studies in which pain was the sole unexplained symptom were excluded.
C. Patients received TMS.
D. A description of symptom severity before and after TMS was given.

When multiple publications included samples that overlapped such that all patients from one publication were described as part of a larger sample in another publication, the publication with the largest sample size was included. When it was unclear whether a publication met the inclusion criteria, consensus was sought between investigators.

Scoring of the quality of the selected studies
General study quality
Selected studies were assessed using a quality score based on that used by Walburn et al.[17] The score aims to cover variables that are felt to be relevant to critical appraisal, although not all variables were relevant to all study designs (especially those lower down in the 'hierarchy of evidence', eg, single case studies[18]). These include:
1. Statement of explicit a priori aims.
2. Definition or description of the size of the population under investigation.
3. Sample size calculation.
4. Justification that the sample is representative of the population.
5. Inclusion and exclusion criteria stated.
6. Demographic details of participants.
7. The research undertaken is independent of routine care or practice.
8. Justification of the reliability and/or the validity of outcome measures.
9. Specification of the response/dropout rate.
10. Justification of the response/dropout rate.
11. Discussion of generalisability of results.
12. Statement of source funding.

TMS protocols
In addition each selected study was assigned a 'TMS methods score' which reflected the amount of detail, and hence the reproducibility, of the TMS protocol in each selected study.

Checklist of TMS parameters (reproducibility score, maximum score=8) include:
1. Coil type
2. Frequency
3. Intensity of stimulation
4. Target area
5. Localisation method
6. Number of stimuli/pulses
7. Number of sessions
8. Duration of treatment.

Studies were also assessed for the following markers of methodological quality:
▸ Inclusion of a control/comparison group
▸ Use of placebo or sham TMS condition
▸ Use of physician-rated outcome measures
▸ Assessors blinded to treatment group.

RESULTS
Ten publications that met the criteria were identified.[19–28] One study was in German;[21] an English-language version of the paper was kindly supplied by the first author. Three papers[23–25] detailed the same group of patients and so the most recent and comprehensive[24] was chosen. Two conference abstracts were identified.[27 28] Where sufficient methodological detail was lacking, authors were contacted by electronic mail for further details.

The study designs, quality scores and outcomes are outlined in table 1.

In total 95 patients received TMS.

There was considerable heterogeneity in terms of population sampled, study design, TMS parameters and outcome measures (table 1).

All the patients in the selected studies had motor symptoms. Overall, 78 patients had weakness (including a case of aphonia in which vocal cord adduction was absent) and 17 had a movement disorder (tremor, blepharospasm, unspecified 'psychogenic movement disorder'). All the patients in the study by Schonfeldt-Lecuona et al[24] (n=4) and 66% (n=46) of the patients in the study by Chastan and Parain[19] also had pain or other sensory symptoms.

Two patients (one in Deftereos et al[26] and one in Schonfeldt-Lecuona et al[24]) were eventually diagnosed with malingering rather than functional (conversion) symptoms. These were included in the review because they met the inclusion criteria insofar as participants had medically unexplained neurological symptoms and subsequently received TMS.

The quality of the studies was generally poor, with only one study[21] achieving more than 50% of the possible marks for quality. None was blinded or placebo controlled. There was often insufficient description of the TMS study design to allow for adequate reproducibility with only one study[21] scoring full marks and some studies not even specifying the total number of TMS pulses used.

No two papers used the same outcome measure and in most studies outcome measures were subjective (eg, the clinician's global clinical impression). An exception in this regard was Dafotakis et al,[21] which used a prospective study design with a clearly reproducible TMS protocol and an objective outcome measure (tremor frequency on kinematic motion analysis), although this study was neither placebo controlled nor blinded.

All except one of the selected studies claimed to show a benefit from the therapeutic use of TMS, although due to differences in outcome measures and duration of follow-up the overall magnitude of this effect could not be quantified. Of these successful studies, with the exception of seven of the

Table 1 Overview of published studies of TMS in the treatment of functional neurological symptoms

Study	Patients	Duration	Target	Protocol	Quality scores	Effects (outcome measure)	Follow-up
Jellinek et al[22]	1 (paresis) Age=25	11 days	Vertex	Single pulse	Overall quality: 2/8 (25%) TMS methods: 5/8	Recovery at 1 week (clinical examination)	Sustained at 1 month
Schonfeldt-Lecuona et al[24]	4 (paresis) Ages=37, 20, 39, 59	5 weeks–5 years	MC	▶ 15 Hz (4000 pulses per session) ▶ 110% motor threshold, then 90% after 2 weeks ▶ 1 session/day for 4–12 weeks	Overall quality: 6/12 (50%) TMS methods: 7/8	3/4 improved (clinical examination) (1 diagnosed feigning)	Sustained at 6–12 months
Deftereos et al[26]	1 (paresis) Age=35	4 years, worsening in last 24 h	MC	▶ Single pulse at 100% stimulator output ▶ 1 session	Overall quality: 1/9 (12.5%) TMS methods: 5/8	Improved (clinical impression) (diagnosed feigning)	NA
Chastan et al[20]	1 (aphonia) Age=18	20 months	MC (and PFC)	▶ 0.33 Hz (30 pulses to PFC and 30 to MC) 2.5T max ▶ 2 sessions 1 week apart (one session PFC, one session MC) Circular coil	Overall quality: 2/8 (25%) TMS methods: 6/8	Improvement within few days (clinical impression)	Sustained at 6 months
Chastan and Parain[19]	70 (paresis) Age=8–79; mean 24.7±16.6	Acute in 55 patients (median duration: 4 days) and subacute/chronic in 15 patients (median duration: 240 days). Overall median duration: 5 days	MC	▶ 0.2–0.25 Hz (30 or 60 pulses) 2.5T max ▶ 1 or 2 sessions on 1 day	Overall quality: 3/12 (25%) TMS methods: 6/8	Effective 89% (immediately or within hours 73%), ineffective 11% (clinical impression)	Recurrence of symptoms in 8 patients after 150–160 days. Repeat rTMS effective in 6
Kresojevic et al[27]	2 (1×paresis Age=52; 1×PMD Age=24)	Not stated	Vertex	▶ 30%–80% of stimulator output ▶ 12 pulses	Overall quality: 1/8 (12.5%) TMS methods: 4/8	Immediate response in both patients (clinical impression)	Recurrence of mild symptoms at 6 months
Dafotakis et al[21]	11 (tremor) Age=24–50; mean 42±9	48±57 months	MC	▶ 0.2 Hz: (30 pulses) ▶ 120% motor threshold for 15, then 140% for 15	Overall quality: 9/12 (75%) TMS methods: 8/8	Mean of 97% immediate reduction in tremor frequency (kinematic motion analysis)	7/11 transient and 4/11 sustained at 8–12 months
Shah et al[28]	5 (PMD) Age not stated	6.2±5.5 years	MC	rTMS for 5 consecutive days (no other details)	Overall quality: 2/12 (17%) TMS methods: 1/8	No change at 2 weeks (quality of life scale; patient and clinician global impression of change)	Not stated

No studies were blinded or placebo controlled.
2.5T max, 2.5 tesla maximum intensity; MC, motor cortex; PFC, prefrontal cortex; PMD, psychogenic movement disorder; rTMS, repetitive TMS; TMS, transcranial magnetic stimulation.

11 patients in Dafotakis *et al*[21] who experienced only a transient improvement in tremor from TMS, the clinical benefit lasted the duration of follow-up (range: 1–12 months).

The one negative study was reported by Shah *et al*[28] as a conference abstract. No improvement was found in quality of life scores, patient rating of change or investigator rating of change 2 weeks after 5 days of rTMS to motor cortex. Unfortunately, the abstract does not specify the rTMS protocol used so it is not possible to speculate whether any features of the study design may have contributed to this exceptional result. Interestingly, the subjects in this study had had symptoms for a mean of 6.2 years ± 5.5 which is the longest mean of those studies which stated duration of illness.

The outcome of sensory symptoms was not generally commented on in the selected studies.

DISCUSSION

The absence of controlled trials or common outcome measures in the selected studies precludes the use of meta-analytic methods and highlights a pressing need for sufficiently large controlled trials of TMS in the treatment of FNS. Although results were generally positive, the variety of TMS protocols used was so great that no firm conclusions can be drawn about the *mechanism* by which TMS, if efficacious, might exert a therapeutic effect.

The following discussion highlights important areas of consideration in the design of therapeutic trials of TMS for FNS.

Necessity for a control condition

No placebo-controlled studies of TMS as a treatment for FNS have been conducted to date. Reviews of the therapeutic uses of rTMS have emphasised the crucial importance of a placebo condition even in small, proof-of-principle studies.[13] There exists considerable debate as to what constitutes an appropriate placebo condition in TMS studies, with many of the proposed methods (eg, a sham coil that makes a similar sound to the real coil but emits no magnetic pulse; a real coil held at a 45° angle from the skull) offering inadequate blinding such that the participant is able to guess which trial arm he or she was in, if asked.[29] This situation is made more problematic still in many of the current studies, as, in contrast to typical rTMS protocols, many studies used suprathreshold stimulation intensities which cause a muscle twitch with each pulse.

Although most of the evidence is anecdotal,[30] some clinicians believe that patients with FNS exhibit a particularly marked placebo response. For example, patients with the fixed dystonia syndrome (a functional movement disorder characterised by fixed contraction of a muscle group, often the hand or foot) sometimes show an immediate response to injections of botulinum toxin[31] (in contrast with patients with primary dystonia in whom a response will usually only be seen after several days). Some patients with psychogenic Parkinsonism show an immediate and sustained response to a number of different placebo modalities.[32] There is some evidence that this relates to greater suggestibility in these patients.[8] The absence of a placebo control condition in the selected studies therefore means that claims of treatment efficacy via a neuromodulatory effect of rTMS should be interpreted with extreme caution in this patient group.

The studies which included patients with an overall long duration of symptoms[21 28] tended to show that TMS was either ineffective or had a transient effect. A study of 70 patients whose duration of symptoms ranged from 1 to 1080 days found that TMS was significantly more effective for acute than subacute/chronic symptoms.[19] Short duration of symptoms is a

positive prognostic factor in studies of FNS generally.[33] It is therefore possible that one reason for patients improving in these studies is that, given the symptoms were of relatively short duration, the patients were likely to get better anyway. Future studies may wish to address this issue by including a natural history (ie, no active intervention) control group.

Choice of TMS protocols

There was significant heterogeneity in the TMS protocols that were used. Seven of eight studies did not supply enough information about these parameters for full reproducibility. Further, none of the publications attempted to justify the particular parameters used.

Single pulse versus rTMS

Studies differed in the kind of TMS used. The earliest included paper,[22] from 1992, used single-pulse TMS as a diagnostic tool (the authors demonstrated normal motor evoked potentials in a patient with a flaccid paraplegia and the patient achieved spontaneous remission 8 days later). Another diagnostic use of single pulse TMS led to a diagnosis of malingering rather than FNS.[26]

Of the six remaining studies, stimulation was given repetitively but the total number of pulses ranged from 12[27] to many tens of thousands.[24] rTMS protocols used to induce neuromodulation typically involve many hundreds or thousands of pulses. Four[19–21 27] of the 'rTMS' studies included here used a total of fewer than 100 pulses. It is doubtful whether the stimulation paradigms in these studies would be sufficient to induce plastic changes in cortical excitability. In the absence of the possibility of genuine neuromodulation, it appears more likely that another mechanism of therapeutic action is needed to explain the apparent successes of these studies (see section 'Potential therapeutic mechanisms of TMS').

Frequency

The frequency of TMS stimulation in the selected studies was less than 1 Hz in all studies except one:[24] stimulation at these frequencies is generally held to have an *inhibitory* effect on cortical excitability (ie, a long-term depression-like effect). There may be some face validity for using an inhibitory stimulation paradigm in psychogenic tremor (as in Dafotakis *et al*[21]), a condition characterised by unwanted excess movement. The rationale for using it in patients with psychogenic paralysis in which there is a *deficit* of movement is less clear and was not justified in the selected papers.

Intensity of stimulation

Intensity of TMS stimulation in motor paradigms is usually defined as a percentage of the resting motor threshold (RMT), the minimum intensity required to produce a motor output from a muscle at rest. As was the case with other stimulation parameters, the studies in this review differed considerably in the stimulation intensity used. Indeed the intensities that were used were inconsistently reported, with some authors using percentage of RMT, others using percentage of maximum stimulator output and still others defining intensity in terms of the strength of magnetic field produced.

Choice of intensity is a crucially important consideration. rTMS protocols that use a suprathreshold intensity (ie, above 100% RMT), by definition, stimulate muscle activity and hence movement, which may be seen or felt (proprioceptively) by the subject. Currently used neuromodulatory rTMS paradigms tend to use *subthreshold* stimulation. It is possible that the success of TMS in FNS may relate to *the demonstration of the possibility*

of movement rather than genuine neuromodulation. Future studies should ensure that the effects of neuromodulation are isolated from those of inducing muscle activity by selecting a subthreshold intensity for any rTMS protocol that is intended to have neuromodulatory effects.

Choice of stimulation target

Six of the eight selected studies stimulated primary motor cortex (M1). Two studies[22 27] stimulated 'above the vertex', which is likely also to correspond to motor cortex stimulation. Shah et al[28] did not state the site of stimulation in their five patients.

The rationale for choosing a particular brain region to stimulate will differ depending on the presumed therapeutic mechanism of TMS. If it is felt that TMS works in these patients by a neuromodulatory process, then there is no reason why other brain regions implicated in the emergence and maintenance of FNS, such as prefrontal or parietal cortex, should not be stimulated. If, however, the demonstration of movement is felt to be therapeutically important, motor cortex is the most logical choice of target.

Outcome measures

Outcome measures used in the selected studies were heterogenous, with an overall lack of objective, physician-rated measures. Clinical experience and recent data suggest that in some FNS there is a mismatch between the perceived and the actual severity of symptomatology.[34] We therefore suggest that in addition to objective ratings of symptom severity, assessments of the efficacy of treatments for FNS include patient-rated measures, including subjective ratings of symptom severity and functional impact as well as quality of life scales.

Potential therapeutic mechanisms of TMS

Due to the poor quality and heterogeneity of the selected studies, the efficacy of TMS in the treatment of FNS cannot be established. Nonetheless, all but one of these studies was positive. If TMS is shown by subsequent controlled studies to exert a genuine therapeutic effect in FNS, it is unclear by what mechanism this might occur. We outline here four possibilities, which are not mutually exclusive.

The neuromodulatory hypothesis

It is possible that the effects of TMS in the current studies are mediated by changes in cortical excitability and/or resultant changes in connectivity between brain areas. This is unlikely for three reasons:

A. The studies selected for this review described therapeutic success despite all but one using TMS protocols that are unlikely to result in significant neuromodulation.
B. The responses to TMS in the selected studies were often dramatic in terms of symptom improvement, which is rare in controlled TMS studies in other conditions.
C. The duration of benefit claimed by some of the selected studies is far longer than that seen in some of the better sham-controlled, blinded trials of rTMS in organic movement disorders such as Parkinson's disease or dystonia, which is rarely longer than a month for multi-session studies and is often in the region of a few hours for single-session studies.[13] These studies also tend to use considerably *more* stimulation (as measured by, eg, total number of pulses) than those selected for the present review. Note that this is only partial evidence against the neuromodulatory hypothesis since it is also consistent with the possibility that FNS patients have *softer*

neurological abnormalities than, for example, Parkinson's disease patients.

The placebo/non-specific effects hypothesis

Since there have been no controlled studies of TMS for FNS, the possibility remains that symptom improvement occurs because of a placebo response. The use of a sham TMS condition would be one way to address this possibility (although this is not entirely unproblematic; see section 'Necessity for a control condition').

The nature of the placebo response is increasingly understood to be highly complex and is influenced by many factors that relate to the therapeutic setting.[35] One important factor in all areas of medicine, but perhaps particularly in treating FNS,[36] is the *expectancy* that the therapeutic encounter generates. In the selected studies it was largely unclear whether the TMS was introduced as purely diagnostic, therapeutic or both. An exception is Dafotakis et al,[21] in which the procedure was explained to patients as a way of establishing the psychogenicity of the disorder, which in turn was expected to have therapeutic value. Shah et al[28] also describe giving rTMS to their patients with a 'strong suggestion of expected benefit'. Future studies should be explicit and consistent about the information given to patients regarding the purpose and possible effects of TMS.

The *possibility of symptom improvement* hypothesis

Motor cortical stimulation produces transient movement effects that occur in contrast to the deficit that characterises the functional (conversion) symptom (eg, movement in a 'paretic' limb or reduction in tremor frequency). The perception (which may be visual, somatosensory or even proprioceptive), on the part of the patient, that symptom improvement is possible may influence regain of function in three ways:

A. By presenting the cognitive system with an opportunity to 'relearn' its normal function
B. By presenting the individual with an opportunity to regain function in an acceptable or 'face-saving' manner
C. By facilitating insight into the psychological mechanisms underlying the disorder (this in turn may influence adherence to particular therapies, eg, CBT[21]).

Consistent with this hypothesis are recent data suggesting that patients with FNS have a core deficit in the *perception* of their actions or bodily states.[34 37] Further, the immediacy of response of many patients in these studies may relate to a cognitive bias whereby patients update their beliefs (eg, 'I can move my arm') based upon significantly less evidence than controls (the 'jumping to conclusions' bias[38]).

Within this account the fundamental therapeutic mechanism involve a change in higher level beliefs or expectations about symptoms. To this extent, the 'active ingredient' in treatment may be comparable with that of targeted CBT or administering botulinum toxin to patients with functional dystonia.

A recent Bayesian account of the development and maintenance of FNS[39] suggests that these symptoms develop when the precision (or certainty) of abnormal intermediate level prior beliefs (or expectations) is enhanced by misdirected, self-focussed attention. Thus, successful treatment of these symptoms involves enhancing the precision or certainty of an incompatible, higher level belief about symptoms—precisely what happens when the possibility of movement is demonstrated to a patient with functional weakness during TMS.

Stone and Edwards have argued[40] that there may be therapeutic benefit in demonstrating to patients with FNS that they have physical signs that are inconsistent with organic neurological illness

(eg, Hoover's sign, in which there is involuntary extension of the 'paralysed' leg when the contralateral leg if flexed against resistance). Thus, signs that were once felt to be 'tricks' to catch out cases of non-organic illness may be put to better use as a method of 'rational persuasion' of the patient that their symptoms can get better just as when the possibility of symptom improvement is demonstrated to the patient via TMS.

It will be important in future work to tease out these components. For example, it may be critical to examine the patient's 'hypotheses' about the nature of their paresis in the case of functional motor symptoms so that TMS-induced movement would provide a useful and convincing test (to them) that recovery is possible. Hence a degree of guided cognitive therapy, explicit or implicit, in conjunction with TMS may be crucial.

The mechanisms which come under hypothesis 3 might be interpreted as complex kinds of placebo response, in that all entail the participant 'witnessing' an improvement in his own symptoms. However, we feel it is useful to distinguish this from a more 'traditional' placebo response, one that occurs from non-specific effects.

The *legitimate medical procedure* hypothesis

Missing from all these cognitive accounts but encompassed in (B) in the previous section is the inter-personal or social effect of TMS. In this case, TMS may provide an esoteric but plausible treatment modality which satisfies the individual's need to show that they have been subject to change by an outside agency and that they have participated in a therapeutic process, so that recovery does not delegitimise their illness.[41]

It is important to note that even if TMS is demonstrated to exert a therapeutic effect through *non-neuromodulatory* mechanisms this does not mean that it is an unsuitable treatment for FNS. Most models of the development and maintenance of FNS involve abnormal belief formation as a fundamental component[39][42] (note that 'belief' in this sense need not always be a consciously reportable proposition accessible to introspection); if TMS works by changing patients' beliefs about their symptoms, then it is acting on a core aetiological component of the disorder and is therefore a highly appropriate therapeutic modality.

Patient selection

There are insufficient patient data reported to draw firm conclusions about whether particular patient characteristics predict a good response to TMS. The studies with the most strongly positive results were those in which subjects had weakness symptoms. Improvement with functional movement disorder symptoms was more often transient[21] or absent.[28]

It is interesting that the study with the most negative results was also the one that included patients with the longest disease duration. Length of disease is a poor prognostic factor in FNS.[33][43] It is therefore important that subsequent proof-of-concept studies of the therapeutic use of TMS use a relatively non-chronic patient cohort.

Some patients had sensory symptoms in addition to motor symptoms. Of these, the sensory symptoms improved in three-fourths of the patients in Schonfeldt-Lecuona *et al*;[24] unfortunately, Chastan and Parain[19] do not comment on the response to treatment of sensory symptoms, which were present in two-thirds of their series of 70 patients.

Another condition in which we suggest TMS may have therapeutic value is in functional or hysterical blindness, where the experience of phosphenes during visual cortex stimulation may act in an analogous manner to experiencing the movement of a 'paretic' limb in re-establishing normal function.

CONCLUSIONS

There is insufficient good quality evidence to establish TMS as an effective treatment modality for FNS. However, of the non-placebo controlled, unblinded studies that have been published to date, nearly all have claimed significant success for the technology. This may strike an initial note of cautious optimism, particularly with regard to functional weakness, and serve as an impetus for the development of larger subsequent trials of greater quality.

We recommend that future studies of TMS as a therapeutic modality in FNS make every effort to adhere to the standards of quality outlined in sections 'General study quality' and 'TMS protocols'. In particular, there is a need for a carefully considered control condition, adequate blinding and use of objective, physician-rated (and also patient-rated) outcome measures. Careful choice of the TMS protocol in each treatment arm will be necessary to elucidate which potential therapeutic mechanisms contribute the largest effect.

REFERENCES

1 Stone J, Carson A, Duncan R, et al. Symptoms 'unexplained by organic disease' in 1144 new neurology out-patients: how often does the diagnosis change at follow-up? *Brain* 2009;132:2878–88.
2 Stone J, Carson A, Duncan R, et al. Who is referred to neurology clinics?—the diagnoses made in 3781 new patients. *Clin Neurol Neurosurg* 2010;112:747–51.
3 Nicholson TR, Stone J, Kanaan RA. Conversion disorder: a problematic diagnosis. *J Neurol Neurosurg Psychiatry* 2011;82:1267–73.
4 Carson AJ, Brown R, David AS, et al. Functional (conversion) neurological symptoms: research since the millennium. *J Neurol Neurosurg Psychiatry* 2012;83:842–50.
5 Cojan Y, Waber L, Carruzzo A, et al. Motor inhibition in hysterical conversion paralysis. *Neuroimage* 2009;47:1026–37.
6 Kanaan RA, Craig TK, Wessely SC, et al. Imaging repressed memories in motor conversion disorder. *Psychosom Med* 2007;69:202–5.
7 Stone J, Zeman A, Simonotto E, et al. FMRI in patients with motor conversion symptoms and controls with simulated weakness. *Psychosom Med* 2007;69:961–9.
8 Bell V, Oakley DA, Halligan PW, et al. Dissociation in hysteria and hypnosis: evidence from cognitive neuroscience. *J Neurol Neurosurg Psychiatry* 2011;82:332–9.
9 Oakley DA. Hypnosis and conversion hysteria: a unifying model. *Cogn Neuropsychiatry* 1999;4:243–65.
10 Goldstein LH, Chalder T, Chigwedere C, et al. Cognitive-behavioral therapy for psychogenic nonepileptic seizures: a pilot RCT. *Neurology* 2010;74:1986–94.
11 Czarnecki K, Thompson JM, Seime R, et al. Functional movement disorders: successful treatment with a physical therapy rehabilitation protocol. *Parkinsonism Relat Disord* 2012;18:247–51.
12 Ruddy R, House A. Psychosocial interventions for conversion disorder. *Cochrane Database of Systematic Reviews* 2005;4:CD005331. doi:10.1002/14651858. CD005331.pub2
13 Edwards MJ, Talelli P, Rothwell JC. Clinical applications of transcranial magnetic stimulation in patients with movement disorders. *Lancet Neurol* 2008;7:827–40.
14 Geraldes R, Coelho M, Rosa MM, et al. Abnormal transcranial magnetic stimulation in a patient with presumed psychogenic paralysis. *J Neurol Neurosurg Psychiatry* 2008;79:1412–13.
15 Liepert J, Hassa T, Tuscher O, et al. Motor excitability during movement imagination and movement observation in psychogenic lower limb paresis. *J Psychosom Res* 2011;70:59–65.
16 Slotema CW, Blom JD, Hoek HW, et al. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry* 2010;71:873–84.

17 Walburn J, Gray R, Gournay K, et al. Systematic review of patient and nurse attitudes to depot antipsychotic medication. Br J Psychiatry 2001;179:300–7.

18 Dalziel K, Round A, Stein K, et al. Do the findings of case series studies vary significantly according to methodological characteristics? Health Technol Assess 2005;9:1–146.

19 Chastan N, Parain D. Psychogenic paralysis and recovery after motor cortex transcranial magnetic stimulation. Mov Disord 2010;25:1501–4.

20 Chastan N, Parain D, Verin E, et al. Psychogenic aphonia: spectacular recovery after motor cortex transcranial magnetic stimulation. J Neurol Neurosurg Psychiatry 2009;80:94.

21 Dafotakis M, Ameli M, Vitinius F, et al. Transcranial magnetic stimulation for psychogenic tremor - a pilot study. Fortschr Neurol Psychiatr 2011;79:226–33.

22 Jellinek DA, Bradford R, Bailey I, et al. The role of motor evoked potentials in the management of hysterical paraplegia: case report. Paraplegia 1992;30:300–2.

23 Schonfeldt-Lecuona C, Connemann BJ, Spitzer M, et al. Transcranial magnetic stimulation in the reversal of motor conversion disorder. Psychother Psychosom 2003;72:286–8.

24 Schonfeldt-Lecuona C, Connemann BJ, Viviani R, et al. Transcranial magnetic stimulation in motor conversion disorder: a short case series. J Clin Neurophysiol 2006;23:472–5.

25 Schonfeldt-Lecuona C, Connemann BJ, Herwig U, et al. Transcranial magnetic stimulation in motor conversion disorder. Eur Psychiat 2005;20:S133–S.

26 Deftereos SN, Panagopoulos GN, Georgonikou DD, et al. Diagnosis of nonorganic monoplegia with single-pulse transcranial magnetic stimulation. Prim Care Companion J Clin Psychiatry 2008;10:414.

27 Kresojevic N, Petrovic I, Tomic A, et al. Transcranial magnetic stimulation in therapy of psychogenic neurological symptoms: two case reports. Mov Disord 2010;25:S220–S.

28 Shah BB, Zurowski M, Chen R, et al. Failure of motor cortex repetitive transcranial magnetic stimulation (rTMS) combined with suggestion in the treatment of chronic psychogenic movement disorders (PMDs): a pilot study. 15th International Congress of Parkinson's Disease and Movement Disorders, Toronto, ON, Canada, 2011.

29 Broadbent HJ, van den Eynde F, Guillaume S, et al. Blinding success of rTMS applied to the dorsolateral prefrontal cortex in randomised sham-controlled trials: a systematic review. World J Biol Psychiatry 2011;12:240–8.

30 Shamy MC. The treatment of psychogenic movement disorders with suggestion is ethically justified. Mov Disord 2010;25:260–4.

31 Edwards MJ, Bhatia KP, Cordivari C. Immediate response to botulinum toxin injections in patients with fixed dystonia. Mov Disord 2011;26:917–18.

32 Jankovic J. Diagnosis and treatment of psychogenic parkinsonism. J Neurol Neurosurg Psychiatry 2011;82:1300–3.

33 Crimlisk HL, Bhatia K, Cope H, et al. Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms. BMJ 1998;316:582–6.

34 Parees I, Saifee TA, Kassavetis P, et al. Believing is perceiving: mismatch between self-report and actigraphy in psychogenic tremor. Brain 2012;135:117–23.

35 Rief W, Bingel U, Schedlowski M, et al. Mechanisms involved in placebo and nocebo responses and implications for drug trials. Clin Pharmacol Ther 2011;90:722–6.

36 Rief W, Broadbent E. Explaining medically unexplained symptoms-models and mechanisms. Clin Psychol Rev 2007;27:821–41.

37 Stone J, Gelauff J, Carson A. A "twist in the tale": altered perception of ankle position in psychogenic dystonia. Mov Disord 2012;27:585–6.

38 Parees I, Kassavetis P, Saifee TA, et al. 'Jumping to conclusions' bias in functional movement disorders. J Neurol Neurosurg Psychiatry 2012;83:460–3.

39 Edwards MJ, Adams RA, Brown H, et al. A Bayesian account of 'hysteria'. Brain 2012;135:3495–512.

40 Stone J, Edwards M. Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signs. Neurology 2012;79:282–4.

41 Taylor DC. Hysteria, play-acting and courage. Br J Psychiatry 1986;149:37–41.

42 Brown RJ. Psychological mechanisms of medically unexplained symptoms: an integrative conceptual model. Psychol Bull 2004;130:793–812.

43 Mace CJ, Trimble MR. Ten-year prognosis of conversion disorder. Br J Psychiatry 1996;169:282–8.

JNNP

A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms

Thomas A Pollak, Timothy R Nicholson, Mark J Edwards and Anthony S David

Updated information and services can be found at:

http://jnnp.bmj.com/content/85/2/191

These include:

References	This article cites 41 articles, 16 of which you can access for free at: http://jnnp.bmj.com/content/85/2/191#BIBL
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes