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Short communication

Repetitive transcranial magnetic stimulation plus standardized suggestion of benefit for functional movement disorders: An open label case series

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ABSTRACT

Background: We studied suggestion of benefit combined with motor cortex and premotor cortex repetitive transcranial magnetic stimulation (rTMS) in chronic (>2 years) FMDs.
Methods: Patients were identified from our patient records who had clinically definite FMDs and had undergone neuropsychiatric evaluation. Those with chronic FMDs were offered open-label rTMS over the dominant motor cortex. If they failed to improve they received dominant premotor cortex rTMS. The primary outcome was change from baseline to post-rTMS in quality of life measured by the World Health Organization Quality of Life Brief (WHOQOL-BREF) scale. Secondary outcomes were subject and investigator global impression of change (GIC), blinded Rush psychogenic movements rating scale, Barbers suggestibility scale, baseline expectation of benefit scale, and adverse effects.
Results: Six subjects were enrolled. For the primary outcome, there was significant improvement in the physical domain scores but significant reduction in psychological domain scores after premotor cortex rTMS compared to baseline and after motor cortex rTMS. There was no significant change between baseline and motor cortex rTMS or in any other domain after premotor cortex rTMS. Secondary outcome measures showed no meaningful change. Transient headache and worsening of FMD symptoms were the most common adverse effects observed.
Conclusion: rTMS combined with strong suggestion of benefit provided dissonant results after premotor cortex rTMS with improvement in physical quality of life but reduction in psychological quality of life. These results serve to underscore the complex nature of FMDs where the overt physical manifestation is but one part of a comprehensive neuropsychological syndrome.

1. Introduction

Functional movement disorders (FMDs; often referred to as "psychogenic" movement disorders) are common in subspecialty and general neurology clinics, accounting for 3–5% of patients seen in movement disorders practices [1]. Psychopathology in these patients varies considerably but anxiety and depression are most common [2], though no primary mood disorder is identifiable in a large portion.

Despite our current ability to diagnose FMDs accurately, the management of these patients has been exceedingly difficult. Many patients continue to manifest symptoms for years [2] with accompanying disability and family disruption, often out of proportion to the degree of observed functional neurologic impairment.

The pathogenic mechanisms underlying FMDs are poorly understood. Imaging studies in other functional neurological disorders have demonstrated disturbances of brain function, including in the motor and premotor cortices, that appear to be reversible when symptoms resolve [3]. It has been hypothesized that physical and emotional triggers can result in neuroplastic changes in the CNS that can, in turn, perpetuate FMDs well after a triggering event has resolved. Results of recent reports have indicated that

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alteration of cortical plasticity via cortical single or paired transcranial magnetic stimulation (TMS) or repetitive trains of stimulation (rTMS) may provide a means of modulating abnormal brain function in the setting of functional neurologic symptoms (FNS) and allow a return to more normal function [4,5]. rTMS directed at either the prefrontal cortical regions or, in the case of some motor disturbances, the primary motor cortex has been proposed as a method of possibly altering and even reversing these changes. To date rTMS use has been investigated for a variety of neurological and psychiatric disorders including Parkinson's disease [6], depression [7,8], and other neuropsychiatric disorders [9] and is an approved treatment for drug-resistant depression in the US and Canada. A recent study of 24 subjects with chronic FMDs found clinical improvement using a low frequency paradigm of stimulation at an intensity above motor threshold [5].

Placebo responses and the associated suggestion of benefit have been well recognized to influence functional neurological disorders [10]. The positive response to placebo has been used not only for the diagnosis of FMDs but also for their treatment. Suggestion of benefit is related to a placebo response, where a subject is intentionally or unintentionally led to believe that an intervention will be beneficial despite the intervention having no physiologic or pharmacologic activity that would adequately treat their condition. Some studies showing benefit or resolution of FNS with rTMS involve patients with short-lived symptoms that may be more sensitive to placebo treatment, early psychological and psychiatric intervention, or a combination thereof [11]. Indeed, studies have shown that the strongest predictor of benefit from any treatment is a short duration of symptoms [12–14].

The aim of this study was to examine the effect of suggestion of benefit with rTMS on improvement of quality of life in subjects with chronic FMDs (greater than 2 years duration of symptoms). This pilot study evaluating effects of both suggestion and rTMS, if positive, would provide rationale for moving to a larger study assessing rTMS with and without suggestion of benefit in delineating whether benefit is gleaned primarily from suggestion of benefit, and thus possibly placebo effect, versus changes in cortical plasticity induced by rTMS.

2. Methods

We performed a two-phase, sequential, open-label study assessing suggestion of benefit combined with rTMS to the dominant motor cortex and subsequently premotor cortex in chronic FMDs. The study was approved by the Research Ethics Board of the University Health Network and all patients provided informed consent.

Patients were identified for participation in the study from our clinic records. All subjects had been previously seen and diagnosed with clinically definite FMD by a movement disorders neurologist (AEL, RC) and had been evaluated by a neuropsychiatrist (MZ). If present, mood disorders had been identified and treated appropriately prior to participation in the study. All of the subjects in the study continued to have disabling movements despite standard of care interventions. Inclusion criteria were diagnosis with clinically definite FMD, symptoms present for over 2 years, and age greater than 18 years. Exclusion criteria were past history of seizures, ongoing treatment with pharmacologic agents which may reduce seizure threshold [15], any history of intracranial surgery, metallic hardware in or located in close proximity to head, pregnant women, and diagnosis with somatization disorder. This last exclusionary criterion was chosen in order to ensure that the FMDs accounted for the majority, if not the entirety, of subjects' morbidity.

Suggestion of benefit of rTMS was introduced at the initial baseline visit and was reinforced at each subsequent study visit by presenting variations of a standard text with elements outlined in E-Table 1. Using a standardized presentation, patients were told that they had a very high likelihood of benefiting from TMS (suggestion of benefit).

All subjects received dominant unilateral motor cortex stimulation in phase 1. Subjects were assessed at 2 weeks after the last day of treatment and if there was benefit, as defined as patient-rated global impression of change (CGI) of 'moderately improved' or 'greatly improved', then subjects were reassessed after 1 month. If there was no benefit or only mild benefit then subjects moved to phase 2, stimulation of the dominant premotor cortex followed by assessment after a further 2 weeks after the treatment phase. A video of every subject was taken at baseline, post-motor cortex stimulation, and post-premotor cortex stimulation assessments. Assessments were done at 2 weeks post stimulation rather than immediately post stimulation to assess for a more durable effect.

In phase 1, rTMS was performed over 5 sessions on consecutive business days. Each session involved using single pulses of TMS over the dominant unilateral motor cortex with a surface EMG of the dominant first dorsal interosseus (FDI) muscle to identify the motor cortical representation of the FDI. The resting motor threshold was determined and was defined as the minimum stimulator output required to produce motor evoked potentials of $\geq$50 μV at least 5 out of 10. rTMS was delivered via a figure-of-eight coil at 0.33 Hz over 150 s (total 50 pulses) at 90% of resting motor threshold. We chose this low-frequency paradigm as it was similar to the previously used parameters in treatment of hyperkinetic FNS. However it is important to note that this paradigm and that used in other rTMS FMD studies have not definitively been shown to have physiologic effects [5]. In phase 2, the procedure was similar to phase 1. However, once the resting motor threshold of the FDI was determined, the figure-of-eight coil was moved 3 cm anterior to the dominant motor cortex in order to stimulate the dominant dorsal premotor cortex. The stimulation parameters were identical to phase 1 and the targeted locations of motor and premotor cortex based on FDI activation are in line with accepted standards for the use of rTMS for most neurologic and psychiatric indications [14].

The primary outcome was change at 2 weeks post treatment in the World Health Organization Quality of Life brief scale (WHOLQOL-BREF), a generic quality of life measure that encompasses four domain scores: physical health, psychological, social relationships, and environment [16].

Secondary outcomes were:

1) Patient and clinician rated global impression of change (GIC) [17] of overall wellbeing.
2) The Barber suggestibility scale [18]; this metric was used to identify patients who may be more suggestible and this was compared with actual benefit (defined by change in primary outcome).
3) A generic expectation of benefit scale developed by the investigators specifically for this study and based on items of the WHOQOL (0–25 point scale, higher scores indicating greater expectation of benefit).

Statistical analysis for the primary outcome measure (domains of the WHOQOL) was done using a Wilcoxon signed rank test using Stata software (StataCorp, College Station, Texas).

3. Results

Six patients were identified and all patients agreed to enroll in the study. E-Table 2 shows demographics, chronicity, and description of their FMD. rTMS was delivered to all subjects between November 2010 and June 2011. All subjects had insufficient benefit with motor cortex stimulation and subsequently had premotor cortex stimulation.

Table 1a shows the results of motor cortex rTMS and premotor cortex rTMS on the four domains of the WHOQOL-BREF. There was significant improvement in the physical domain from baseline to follow-up after motor cortex rTMS and from assessment following motor cortex stimulation to follow-up after premotor cortex stimulation. However, there was a significant decrease in the psychological domain score after premotor cortex stimulation. No significant change was seen in any domains after motor cortex stimulation or in the social relationship and environmental domains after premotor cortex stimulation. Individual results for each domain are shown in Fig. 1.

Secondary outcome results are shown in Tables 1b and 1c. Only one subject noted substantial improvement after premotor cortex stimulation on patient GIC. Other subjects noted minimal change (either improvement or worsening) or no change at all. Also, there was no apparent relationship between pre-treatment suggestibility as measured by the Barber susceptibility scale and change in quality of life after treatment (Fig. 2).

Adverse effects (AE) seen are shown in E-table 3. No persistent adverse effects were seen.

It is worth noting that two subjects (subjects 3 and 5) presented to the clinic many months after the trial and reported persistent and continuing improvement in their overall well-being after premotor cortex stimulation. However, one of these subjects did not attribute her improvement to rTMS.