Multiple sessions of low-frequency repetitive transcranial magnetic stimulation in focal hand dystonia: clinical and physiological effects

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Abstract.
Purpose: The ability of low-frequency repetitive transcranial magnetic stimulation (rTMS) to enhance intracortical inhibition has motivated its use as a potential therapeutic intervention in focal hand dystonia (FHD). In this preliminary investigation, we assessed the physiologic and behavioral effects of multiple sessions of rTMS in FHD.
Methods: 12 patients with FHD underwent five daily-sessions of 1 Hz rTMS to contralateral dorsal premotor cortex (dPMC). Patients held a pencil and made movements that did not elicit dystonic symptoms during rTMS. We hypothesized that an active but non-dystonic motor state would increase beneficial effects of rTMS. Five additional patients received sham-rTMS protocol. The area under curve (AUC) of the motor evoked potentials and the cortical silent period (CSP) were measured to assess changes in corticospinal excitability and intracortical inhibition, respectively. Behavioral measures included pen force and velocity during handwriting and subjective report.
Results: Multiple-session rTMS strengthened intracortical inhibition causing a prolongation of CSP after 3 days of intervention and pen force was reduced at day 1 and 5, leaving other measures unchanged. 68% of patients self-reported as 'responders' at day 5, and 58% at follow-up. Age predicted responders.
Conclusions: A strong therapeutic potential of this rTMS paradigm in FHD was not supported but findings warrant further investigation.

Keywords: Focal hand dystonia, rehabilitation, rTMS, writer's cramp, clinical

1. Introduction

The possibility to induce lasting changes in cortical excitability has motivated the investigation of repetitive transcranial magnetic stimulation (rTMS) as a therapeutic tool in a growing number of clinical applications (for review Edwards et al. 2008). The virtue of low-frequency rTMS to strengthen inhibition (Chen et al. 1997) has motivated its application in focal hand dystonia (FHD), a movement disorder associated with deficient inhibition throughout the central nervous system (for review Berardelli et al. 1998) including the motor cortex (Quartarone et al. 2003). FHD is an idiopathic neurological disorder of movement

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characterized by involuntary co-contractions of agonist and antagonist hand and forearm muscles that are sustained or repetitive (Sheehy and Marsden 1982). FHD can affect any voluntary muscle or group of muscles in the affected limb and is triggered primarily during specific tasks such as handwriting or playing a musical instrument (i.e., task-specific FHD).

Several studies have shown that low-frequency rTMS can alter deficient intracortical inhibition in the primary motor cortex (Siebner et al., 1999b, 1999c; Murase et al., 2005). Murase and colleagues (2005) compared the excitability of intracortical inhibitory circuits in the primary motor cortex (M1) as measured by cortical silent period (CSP) and hand-writing performance before and after low-frequency rTMS (0.2 Hz) applied to the contralateral (left) M1, supplementary motor area (SMA), dorsal premotor cortex (dPMC), and sham stimulation. The highest success rate in terms of clinical improvement, decrease in pen force and increase in intracortical inhibition was observed after dPMC stimulation (Murase et al., 2005). Targeting the dPMC is reasonable as this region plays an important role in movement selection (Schluter et al., 2001) and is abnormally activated in imaging studies in patients with FHD (Ibanez et al., 1999).

A recent study applied 1 Hz rTMS repeatedly over five days (900 pulses/day) in subjects with FHD rather than a single rTMS session (Borich et al., 2009). Compared to sham stimulation, this rTMS protocol reduced intracortical inhibition and improved hand-writing velocity. These effects persisted for ten days following intervention, but clinical improvements were subtle (Borich et al., 2009).

There is converging evidence that the physiological and behavioral effects of rTMS critically depend on the "neural state" of the cortical area at the time of stimulation (Siebner and Rothwell 2003; Ziemann et al., 2008). Based on the acute effects of occipital TMS on visual perception, it has been proposed that rTMS preferentially affects the attributes encoded by less active neural populations (Silvanto et al., 2007a, 2007b). We thus applied interventional rTMS while patients performed writing movements that did not trigger their dystonic symptoms to produce an active but non-dystonic motor state. We speculated that in this state, the "dystonic" neural populations (i.e., the populations producing FHD) would be less active than the normally functioning "non-dystonic" neural populations and thus, would be *more* susceptible to the inhibitory effects of rTMS. This hypothesis is supported by an

rTMS study in which a single intervention of 30 min inhibitory rTMS was applied to M1 while patients performed "nonsense" scribbling (without inducing symptoms) (Siebner et al., 1999b). In that study, 1 Hz rTMS during "nonsense" writing reinforced intracortical inhibition and induced a short-lasting improvement in circle drawing. In this preliminary investigation, we adopted a multi-session approach and performed repeated applications of inhibitory 1 Hz rTMS to the contralateral dPMC during non-dystonic writing motion. The goals of this study were: to assess clinical changes and investigate neurophysiologic responses to rTMS of the activated motor system in patients with FHD.

2. Methods

2.1. Subjects

17 subjects with task-specific FHD (age: 46.5 ± 12.4 y) were studied. Due to the preliminary nature of the investigation, a sample of convenience with 5 subjects was used to test the protocol with a sham-rTMS intervention. Subjects were recruited from local clinics and web sites. The clinical history and physical exam of subjects is reported in Table 1 (Sheehy and Marsden 1982). Exclusion criteria were: (1) any neurologic condition other than FHD, (2) medication for dystonia, (3) botulinum toxin within the past three months, (4) seizure history, (5) pregnancy or (6) implanted medical devices (Rossi et al., 2009). All subjects gave written informed consent prior to participation according to the Declaration of Helsinki. The study was approved by the University of Minnesota General Clinical Research Center and Institutional Review Board.

2.2. Study design

Subjects in the real intervention group ($n = 12$) received only the real rTMS protocol with 10 day follow-up. Subjects in the sham group ($n = 5$) were blinded to group assignment (Figure 1). These subjects were told there were two different levels of stimulation being tested. They initially received the sham stimulation paradigm and then crossed over to the real intervention protocol following the ten-day follow-up. However, due to possible contamination of results due to order effects, the results from the real intervention in the cross-over subgroup were not included in the real group analysis.

Table 1
Clinical and demographic information for subjects with dystonia

Case	Group	Sex	Age	Hand	Duration of sx	Diagnosis	Clinical pattern	Toxin Hx
1	Sham	F	64	R	21yr	WC R	R 3rd digit flexion during writing and typing	Y, 1yr prior
2	Real	M	63	R	7yr	MD R	R 3rd, 4th digit flexion during piano playing, writing, typing	Y, 2yr prior
3	Real	M	41	L	3yr	MD R	R 4th, 5th digit flexion during writing, guitar playing	Y, 1.5yr prior
4	Real	M	68	L	5yr	WC L	L 2nd-4 digit abnormal posturing during writing/typing	N
5	Sham	M	46	R	6yr	WC R	R grip, wrist extensor spasms during writing/typing	Y, 3mo prior
6	Real	M	50	R	2.5yr	WC R	R 2nd-3rd digit abnormal posturing during writing/calculator use	Y, 3mo prior
7	Real	M	59	R	37yr	WC R	R 3rd digit abnormal posturing during writing/golfing	N
8	Real	M	50	R	8yr	WC R	R 3rd digit abnormal posturing during writing/suturing/card dealing	Y, 5yr prior
9	Sham	M	42	R	14yr	MD R	2nd/3rd digit spasm during typing and classical guitar playing	N
10	Sham	M	55	L	9yr	MD L	L 2nd digit flexion playing piano	N
11	Real	F	49	R	5yr	MD R	R 5th digit extension during guitar picking/piano/writing/typing	N
12	Real	F	67	R	2.5yr	WC R	R hand abnormal flexion/tremor during writing/mousing	Y, 1yr prior
13	Sham	F	55	R	12yr	WC R	R hand abnormal flexion/tremor during writing/mousing/pinching	N
14	Real	F	72	R	50yr	WC R	R 2nd-4th digit abnormal posturing during writing/mousing/typing	Y, 5yr prior
15	Real	F	38	R	7mo	WC R	R hand abnormal posturing during writing	N
16	Real	F	61	R	25yr	WC R	R hand abnormal posturing/cramping during writing/carpentry	Y,14yr prior
17	Real	M	42	R	3yr	WC R	R hand abnormal posturing/fatigue during writing and typing	Y, 6mo prior

M = male, F = female, R = right, L = left, WC = writer's cramp, MD = musician's dystonia.

The intervention protocol consisted of one rTMS session (real or sham) given to the contralateral dPMC performed daily for five consecutive days. The primary behavioral measure was axial pen force and velocity during writing. Cortical excitability assessments were collected to assess changes in neurophysiologic response. Subjective symptom report was collected via phone interview after 10 days posttest.

2.3. Handwriting analysis

Handwriting analysis was performed following TMS testing using a computerized tablet (WACOM Co., Ltd, Japan), custom modified digitized pen and Oasis hardware and software package for data collection and analysis (UltraPen, Kiko Software, Doetinchem, The Netherlands). Subjects were instructed to write in their natural, self-paced style the sentence: 'My country tis of thee,' and perform a loop tracing condition. Each condition was repeated 4 times. Data were sampled at 215 Hz (resolution: 5,080 lpi, accuracy: ± 0.01" pressure range: 0–800 g). Mean axial pen force and velocity were the functional variables of interest. Handwriting was assessed after one and five rTMS sessions.

2.4. Assessment of cortical excitability

The primary time point of interest for all measures was results after five days of intervention. However,

changes in excitability over time were also assessed to understand the evolution of the individual's electrophysiology. Thus, single pulse TMS assessments were taken after session 1, 3, and 5, whereas hand-writing was assessed after session 1 and 5 only. Subjects were seated comfortably in a reclining chair. Surface electrodes were affixed to the skin overlying the first dorsal interosseus (FDI) muscle of the involved hand using a belly/tendon montage. The electromyographic (EMG) activity of the resting FDI muscle was recorded at a sampling rate of 2560 Hz using a Cadwell Sierra EMG amplifier (Cadwell Laboratory, Washington) (sensitivity: 100 μv/div, filter: 20–2000 Hz). The EMG collected for each trial was 250 ms in duration, with 25 ms recorded prior to stimulus to assess pre-stimulus activity. Complete absence of pre-MEP activity was ensured by visual inspection during resting TMS data collection and verified during off-line analysis. Trials with >10 μV were excluded from analysis. TMS was performed with a 70-mm figure-of-eight coil connected to a Magstim 200 Rapid magnetic stimulator (Magstim Co., Whitland, Dyfed, UK). The handle of the coil was directed posterolaterally 45° to the mid-sagittal line of the head producing a posterior-anterior current flow in the brain (Orth and Rothwell 2004). We first determined the resting motor threshold (RMT), defined as the minimum intensity required to elicit MEP amplitude >50 μV peak-to-peak in at least 3/5 trials in the resting target muscle (Rossini et al., 1999) which was used to determine the intensity
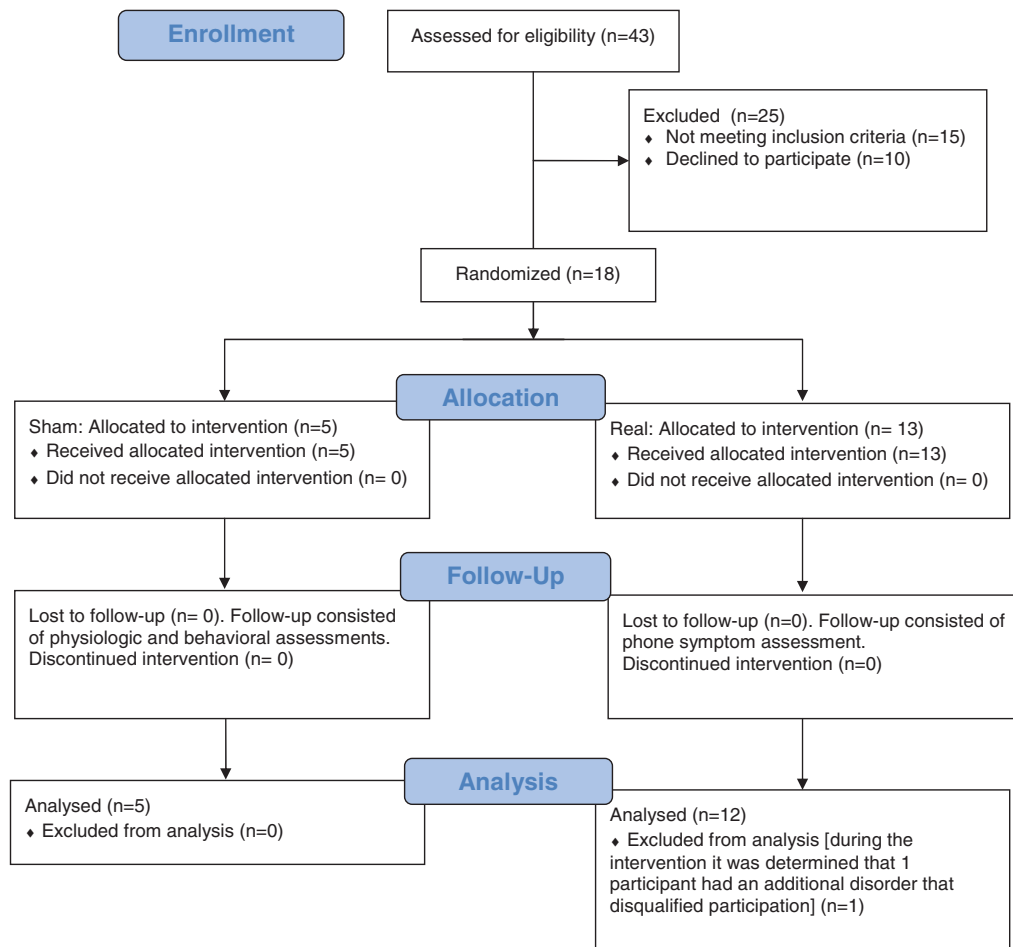
Enrollment

Assessed for eligibility (n=43)

Excluded (n=25)
- Not meeting inclusion criteria (n=15)
- Declined to participate (n=10)

Randomized (n=18)

Allocation

Sham: Allocated to intervention (n=5)
- Received allocated intervention (n=5)
- Did not receive allocated intervention (n= 0)

Real: Allocated to intervention (n= 13)
- Received allocated intervention (n=13)
- Did not receive allocated intervention (n= 0)

Follow-Up

Lost to follow-up (n= 0). Follow-up consisted of physiologic and behavioral assessments. Discontinued intervention (n= 0)

Lost to follow-up (n=0). Follow-up consisted of phone symptom assessment. Discontinued intervention (n=0)

Analysis

Analysed (n=5)
- Excluded from analysis (n=0)

Analysed (n=12)
- Excluded from analysis [during the intervention it was determined that 1 participant had an additional disorder that disqualified participation] (n=1)

Fig. 1. Consort diagram demonstrating flow of subjects through study.

of stimulation for the single-pulse testing. The RMT was recalculated at each testing session with minimal variability between subjects [mean RMT: 48.1% max stimulator output, mean within subject SD 1.59% (range: 0–4.35%), CV = 0.04].

The relation between increasing stimulus intensity and increase in MEP amplitude was assessed with TMS of M1 contralateral to the tested hand. MEP data were collected at intensities of 110, 120, 130, and 140% of RMT with a repetition rate of <0.1 Hz. Five trials were collected at each intensity in a pseudorandom order (gain: 200–500 μv/div, filter: 20–2000 Hz). The linear relationship between mean MEP amplitude and stimulus intensity was analyzed by calculating the slope and area under the curve (AUC) for each subject for each day. The area under the curve (AUC) was calculated through the integral of the linear line of best fit for

the mean data points of each subject across the entire intensity range.

For CSP recording, IFCN committee guidelines were followed (Groppa et al., 2012a). Subjects performed an isometric abduction contraction of the index finger against a strain gauge coupled to a load cell. Force was transduced into an electrical signal displayed on an oscilloscope placed in front of the subject. Subjects were asked to produce a constant force at 20% of maximum voluntary isometric contraction marked on the screen, until instructed to relax. A single TMS pulse was applied 2-3 s after contraction initiation and subjects were instructed to relax 2-3 s after stimulation. Eight trials were recorded with a minimum 20 s rest interval between each trial. The duration of the CSP was measured on a trial-by-trial basis and was delineated by the first superimposed TMS-evoked EMG

spike (onset) and the return of activity to 50% of prestimulus EMG signal (offset) (Siebner et al., 2000; Kimberley et al., 2009). The mean CSP duration was calculated for each block of measurements. The duration of CSP is thought to be related to intracortical GABAergic synapse-mediated inhibition in the stimulated cortical region (Inghilleri et al., 1993; Chen and Hallett 1999). Measures of CSP have been shown to be reliable in repeated measures studies to determine an effect of intervention within a group of subjects (Orth and Rothwell 2004; Borich et al., 2009).

2.5. Subjective symptom and safety assessment

Subjects rated their perceived symptom change using a Likert scale (-3 = significant worsening, 0 = no change, 1 = mild, 2 = moderate/clinically meaningful, 3 = significant improvement). An adverse events questionnaire was administered prior to and after each session, as well as at follow-up.

2.6. rTMS intervention

In each rTMS session, 1800 biphasic stimuli were given to the dPMC in the hemisphere contralateral to the dystonic hand. Low-frequency rTMS (1 Hz) was administered using a figure-of-eight coil (Magstim Rapid[2], Magstim Co., Whitland, Dyfed, UK). The stimulation site for dPMC was defined as 2 cm anterior and 1 cm medial to the previously defined hotspot for FDI activation. This site was chosen based on localization from a previous PET studies (Fink et al. 1997; Schluter et al. 1998) and previous FHD intervention studies (Murase et al. 2005; Borich et al. 2009). In real-rTMS sessions, stimulus intensity was set at 90% of RMT. In the sham-rTMS sessions, all stimulation variables were identical but the coil was held orthogonally to the head to prevent biological effects of stimulation delivery to the head (Lisanby et al. 2001).

During the intervention, subjects were seated in a reclining chair with feet elevated. The stimulation was delivered while patients engaged in an active motor task that did not trigger their dystonic symptoms. This task varied based on each individual's severity of symptoms. Subjects were instructed to hold a 'built-up' pencil in their natural grip and place the tip to paper if possible without triggering any dystonia symptoms. If this was possible, they were then instructed to perform "nonsense" scribbling movements. Subjects were queried regarding possible dystonic symptoms and monitored for dystonic posturing by investigators. Three subjects were unable to put pencil to paper without eliciting symptoms, thus they held the pencil and drew in the air above the paper.

2.7. Statistical analysis

To compare the effects of real- to sham-rTMS interventions multivariate linear mixed effects regression models were implemented using the SAS PROC MIXED procedure (SAS Institute, Cary, NC). This model has the benefit of accounting for missing data, thus addressing the unequal sample sizes between the two groups. Dependent variables of the mixed effects model including slope, AUC, change from baseline in CSP, handwriting pressure and velocity. Independent variables included baseline, group, day and the interaction of group and day. Repeated statement was used to account for the correlation from repeated measures within each subject and treatment. The overall treatment effect by day was evaluated by a Type 3 test. The difference in least square means between TMS and control and its *p*-value were calculated for each day. Subjective symptom change was reported qualitatively and was used to determine "responder" or "non-responder". A criterion for responder was set as a rating of 2 or greater. Binary logistic regression was then performed with the dependent variable 'responder' to examine potential measures that could predict a responder vs. non-responder.

3. Results

All patients tolerated the experimental procedures well without major adverse events. Two patients reported mild headache after a real rTMS intervention and one patient noticed fatigue.

3.1. Single-pulse TMS assessment

Assessment of excitability changes from baseline revealed an increase in excitability of intracortical circuits generating the CSP (Fig. 2C) while having no consistent effects on the slope or AUC (Fig. 2D), reflective of general corticospinal excitability.

Compared to baseline, mean CSP duration increased by 19 ms (18% change) after three days of real rTMS. While there was still a numerical increase in CSP duration, this increase was not statistically
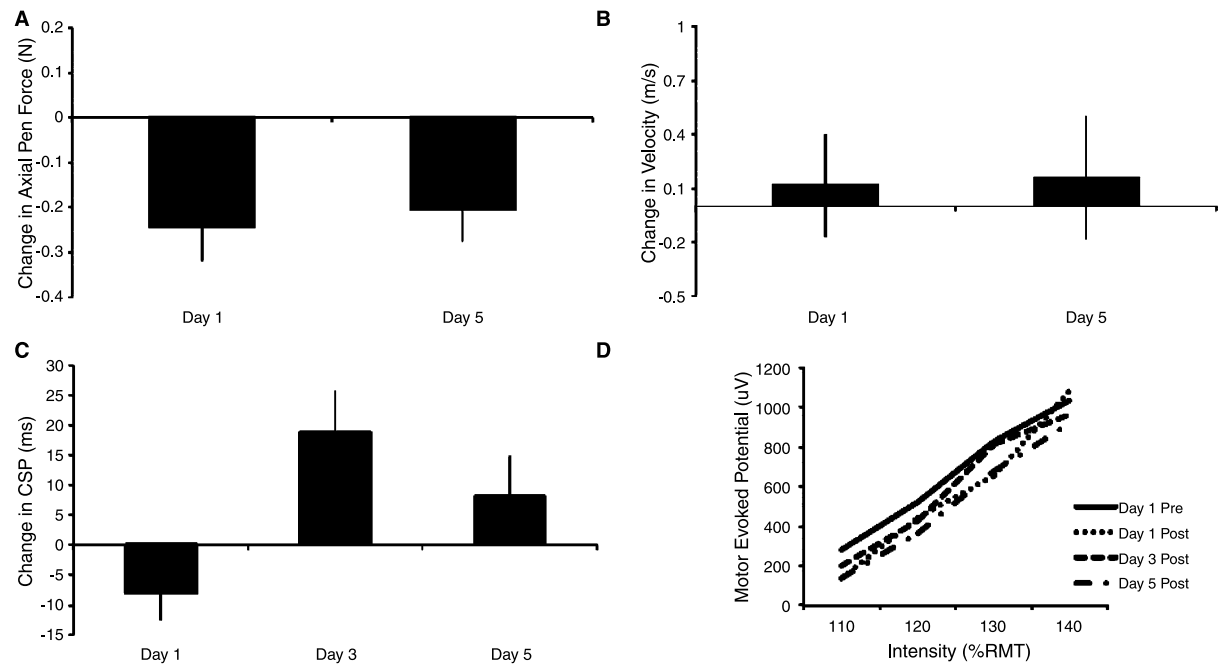
Fig. 2. Outcome measures from group receiving real stimulation [mean (SE), $n = 12$]. A. Mean change axial pen force from baseline (SE) was reduced, Day 1: -0.25 (0.08) N, $p = 0.043$ that was maintained until Day 5: -0.21 (0.07) N, $p = 0.018$. B. Change in velocity from baseline with no differences found. C. Change in cortical silent period (CSP). There was a significant effect of day ($p = 0.029$) with demonstrated lengthening of the silent period between day 1 and 3 of 19.0 (9.2) ms ($p = 0.0054$). D. Slope of Stimulus/Response for single pulse measures at $110 - 140\%$ resting motor threshold. Demonstrated is an apparent reduction in slope but no significant differences across day.

Table 2
Cortical silent period mean values

	Baseline (ms)	Day 1			Day 3			Day 5		
		CSP (ms)	ΔCSP (ms)	% change	CSP (ms)	ΔCSP (ms)	% change	CSP (ms)	ΔCSP (ms)	% change
Sham	117.34 (17.7)	115.29 (18.4)	−2.06 (10.1)	−1.75	120.61 (12.0)	3.27 (6.8)	2.79	118.95 (20.2)	1.61 (15.7)	1.4
Real	106.30 (7.5)	98.45 (9.7)	−7.85 (4.5)	−7.34	117.28 (6.4)	18.77 (7.0)	17.66	106.24 (7.1)	8 (6.9)	7.5

significant on day 5 (7.5% change). In the comparison between groups, there was a significant effect of group ($F = 6.01$, $p = 0.02$). Type 3 tests within the Real group revealed a significant effect of Day ($t = 3.29$, df = 41, $p = 0.029$), with a pairwise comparison difference between Day 1 and 3 ($t = -2.94$, df = 41, $p = 0.0054$). There was no change in the sham group. CSP baseline values, change scores and the mean percent change from baseline is reported in Table 2.

Multivariate linear mixed effects regression models did not demonstrate a significant effect of group. Within the individual groups there was no effect of visit on the slope ($F = 0.304$, df = 3, $p = 0.82$) or AUC ($F = 0.38$, df = 3, $p = 0.77$). This suggests that the intervention did not induce consistent shifts in the gain function of corticospinal excitability, that is, the

relative increase in MEP amplitude with increasing stimulus intensity (Fig. 2D).

3.2. Handwriting analysis

There was a significant effect of baseline axial pen force ($t = -2.45$, df = 12, $p = 0.031$) and a group x day interaction on day 5 ($t = -2.09$, df = 12, $p = 0.047$). When each group was evaluated separately, there was no change across sessions in the sham-rTMS group or in the real-rTMS group for writing velocity (Fig. 2B). However, a significant reduction in axial pen force was found across sessions following real rTMS. Type 3 test revealed a significant effect of day ($F = 3.29$, $p = 0.029$) and differences in least squares means demonstrated a reduction after the first
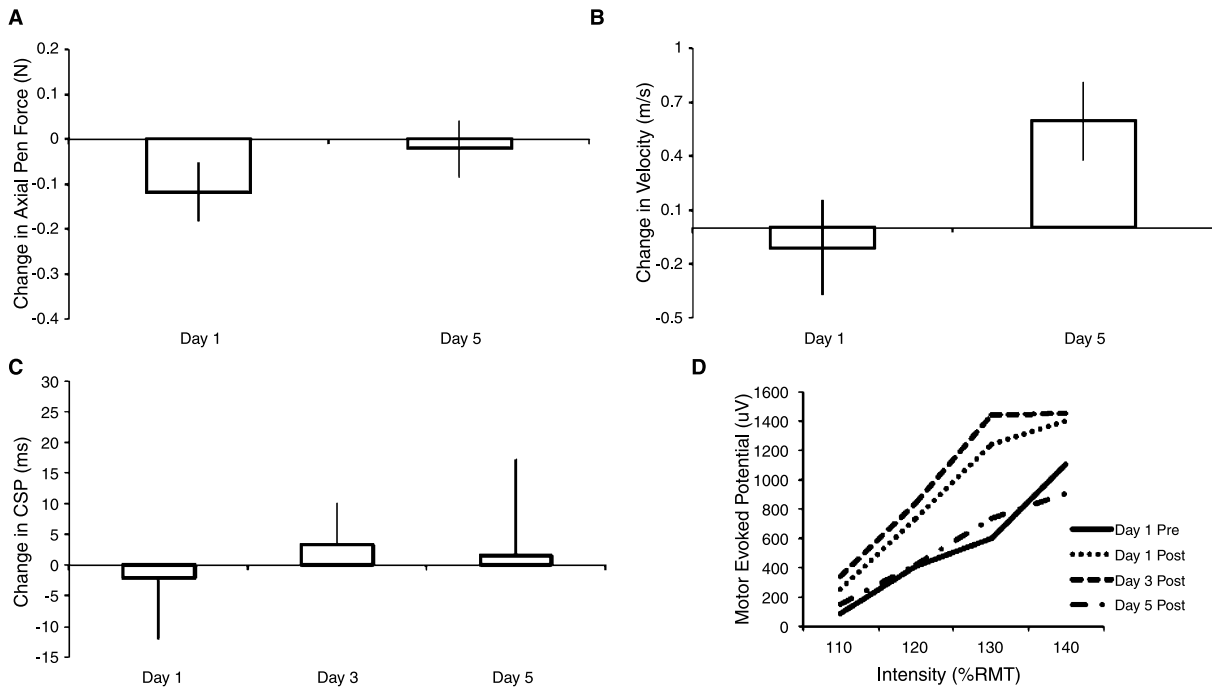
Fig. 3. Outcome measures from group receiving sham stimulation [mean (SE), $n = 5$]. A. Change in axial pen force from baseline. B. Change in velocity from baseline. C. Change in cortical silent period (CSP). D. Slope of Stimulus/Response for single pulse measures at 110 – 140% resting motor threshold. There were no significant differences in the sham group.

real-rTMS intervention (-0.24 N, $t = 2.32$, $p = 0.043$) that was maintained at the conclusion of the interventional period (-0.21 N, $t = -2.54$, $p = 0.018$)(Fig. 2A).

3.3. Effects of sham rTMS

Data are reported for the 5 subjects who received sham stimulation for qualitative comparison across day (Fig. 3). No subjects reported being aware the intervention was sham. In a qualitative assessment of AUC, there is a distinct increase observable at posttest day 1 and 3.

3.4. Subjective report

Subjects were considered a 'responder' if they reported a change ≥ 2. Some subjects in the sham group reported changes between 0-1, but no subjects were considered 'responders' during the sham intervention phase. In the real rTMS group, a total of 58% of subjects were responders for at least 1 session. At Day 1 and 3 there were 4 responders, Day 5 there were 8 and at Day 15, 7 responders. Aside from the planned assessments, 3 subjects contacted investigators to inquire

if they may participate again, as they reported meaningful symptom improvements that lasted for several months.

3.5. Regression analysis

Binary logistic regression of 'responder' ($n = 8$) with the following covariates was assessed in two ways. First, an analysis of response with only age and duration of symptoms was run to determine if demographic information could predict response. Second, day 1 change was added to the prediction model. In a stepwise method: age, symptom duration, day 1 change in CSP, baseline CSP and day 1 change in axial pen force, and baseline AUC, were analyzed. For the purposes of the regression analysis, a subject was classified a 'responder' if they met the set criterion at day 3 or 5. For the first analysis, a significant model was found with age and symptom duration as covariates (Chi-square 4.12, $p = 0.048$, Cox & Snell pseudo $R^2 = 0.300$). This model predicted the correct response 82.4% of time. This suggests that increasing age and symptom duration negatively predicts responder. Interestingly, the model was also significant with only age as a predictor

(Chi-square 4.12, $p = 0.042$). In the second regression assessment the additional measured variables were included stepwise into the model. When additional covariates were added, the model failed to reach significance. Additionally, when any dependent measure or combination of measures was used without age, no significant prediction occurred.

4. Discussion

The use of rTMS as a potential therapeutic agent in dystonia is attractive because rTMS is non-invasive and can reinforce intracortical inhibition known to be dysfunctional in FHD (Siebner et al., 2003; Huang et al., 2004). The majority of studies to date have investigated a single application of stimulation to assess potential effects. Adopting a multi-session approach, this preliminary investigation failed to support our hypothesis that a five-day course of 1 Hz rTMS to the dPMC contralateral to the dystonic hand during non-symptom inducing writing would produce physiological or clinically meaningful changes, however, noteworthy effects were observed. The repeated sessions of rTMS (1) strengthened intracortical inhibition, albeit transiently, as indicated by a longer duration of the CSP peaking after 3 days of stimulation and (2) induced a significant change in handwriting. Patients exerted less pen force during a standardized writing task without changing writing velocity, which was not seen in the sham group. This change corresponded to over half the individuals reporting clinical symptom improvement. Finally, logistic regression identified the age of the patient as the strongest predictor of clinical response to the rTMS intervention.

In the present study, the prolongation in CSP peaked after 3 days of stimulation and became less consistent after completion of the intervention. This speaks against the notion that the reinforcing effects of repeated low-frequency rTMS on intracortical inhibition simply accumulate over time with the number of applications, at least when delivered daily. Although our protocol strengthened intracortical inhibition at the cortical level, this reinforcement did not correspond to the behavioral change. Specifically, at post intervention assessment on day 1, there was a decrease in handwriting pressure and a decrease in CSP indicating *decreased* intracortical inhibition; and at day 5, there was significant handwriting pressure reduction, but not a significant CSP change. As mentioned

previously, handwriting was not assessed at Day 3, so conclusions about this increase can't be directly drawn. It is interesting to note the apparent increase in sham AUC that is not observed in the real group. Though not assessed statistically, this could suggest that the rTMS prevented the increase observed in the sham. This is an area for future investigation. Overall, there appears to be dissociation between these measures which suggests that the link between the level of intracortical inhibition as measured by a single TMS paradigm and the severity of clinical symptoms might not be strong. Thus, the change in CSP duration may not be useful in predicting the clinical efficacy of an interventional rTMS protocol. Change in handwriting pressure has been reported by others following rTMS (Siebner et al., 1999a) and other therapeutic interventions (Zeuner et al., 2008). Whether the increased pressure in subjects with dystonia is measuring the dystonic impairment of handwriting or a compensatory strategy to stabilize the tip of the pen on the tablet during handwriting remains unclear (Zeuner et al. 2007). However, our results do suggests that the axial writing pressure represents a measure that is sensitive to changes in handwriting induced by interventional protocols in FHD.

The novel feature of the present study was to apply rTMS to left dPMC for 5 consecutive days during a non-dystonic motor task. Patients were asked to produce nonsense writing movements while holding a pen in their dystonic hand, but to avoid any symptoms. The rationale behind applying rTMS during an active, non-dystonic state was to more specifically target the motor circuits that produce the dystonic movements (Siebner et al., 1999a). It is possible that our hypothesis was incorrect, and this in fact *reduced* responsiveness. Indeed recent work has demonstrated that motor activity prior or during theta-burst stimulation to M1 can modify the stimulation-induced effects on corticosponal excitability (Gentner et al., 2008; Huang et al., 2008). It is also possible that since the active task required a certain degree of sensory awareness training to ensure lack of dystonic cramping, this could have influenced the effects of the rTMS alone. Further, although we visually monitored for lack of dystonic cramping, it is possible that low level of dystonic cramping did occur during the task. Another study used dual-site TMS to test state-dependent modulation of premotor-to-motor inhibition in FHD. Patients with FHD, but not healthy controls, expressed premotor-to-motor inhibition at rest while this form of inhibition was absent during movement in both groups

(Beck et al., 2009). Therefore, it might be reasonable to first reinstate normal premotor-to-motor inhibition at rest in FHD before trying to influence motor circuits in an active motor state. One might also argue for the opposite strategy by applying rTMS in the presence of dystonia. During the presence of dystonia, deficient inhibition is most obvious and thus, the inhibitory effects might more specifically reinforce inhibition in those circuits subserving dystonia.

In this preliminary study, there were subjects with different types of hand dystonia and large range of symptom duration. An ideal study would have sufficient *n* to be able to stratify subjects within various groups. Another strategy shown to be effective for determining effects in studies with small n is the single subject design analysis (Kimberley and Di Fabio 2010). These studies would help evaluate subpopulations of FHD that are most likely to benefit from rTMS intervention.

It is also important to note, that although a robust effect was not observed in our measures, eight subjects reported "mild-moderate improvement" during the intervention week and seven subjects reported persisting improvement for at least ten days. No improvements in symptom rating were observed for subjects in the sham group at follow-up.

Interestingly, age was the strongest factor assessed that was associated with predicting responders to the intervention. Age was negatively associated with responder to the rTMS intervention paradigm, such that the older the subject: the less likely to be a responder. The strength of the model increased when adding symptom duration and change in CSP from baseline. The reason for age of subject to be a significant predictor of response is beyond the scope of this investigation but may be due to issues of decreasing neuroplasticity with age (Hutchinson et al., 2002).

In conclusion, though the primary goal of the investigation to produce a robust effect in FHD was not achieved, results do demonstrate short-term changes in behavioral, physiologic and clinical measures that support further inquiry into the therapeutic potential of rTMS for individuals with FHD. Future work should explore various parameters of stimulation delivery when investigating the relationship between rTMS, cortical neurophysiology and behavior in FHD and employ other measures of intracortical excitability (e.g. paired pulse assessment of intracortical excitability cortico-cortico excitability with dual-site TMS (Groppa et al., 2012b). Lastly, the salient patient characteristics associated with positive response to rTMS merits further inquiry.

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Financial disclosure/conflict of interest

No authors have any conflict of interest.

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