Published in final edited form as:
Mov Disord. 2010 April 30; 25(6): 696–703. doi:10.1002/mds.22814.

Restoration of motor inhibition through an abnormal premotor-motor connection in dystonia

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Abstract

To clarify the rationale for using rTMS of dorsal premotor cortex (PMd) to treat dystonia, we examined how the motor system reacts to an inhibitory form of rTMS applied to the PMd in healthy subjects and in a group of patients with focal hand dystonia and DYT1 gene carriers. Continuous theta burst transcranial magnetic stimulation (cTBS) with 300 and 600 pulses (cTBS300 and cTBS600) was applied to PMd and its after-effects were quantified by measuring the amplitude of MEPs evoked by single pulse transcranial magnetic stimulation (TMS) over the primary motor cortex (M1), short interval intracortical inhibition/facilitation (SICI/ICF) within M1, the third phase of spinal reciprocal inhibition (RI) and writing tests. In addition, in DYT1 gene carriers, the effects of cTBS300 over M1 and PMd on MEPs were studied in separate experiments. In healthy subjects cTBS300 and cTBS600 over PMd suppressed MEPs for 30min or more and cTBS600 decreased SICI and RI. In contrast, neither form of cTBS over PMd had any significant effect on MEPs, while cTBS600 increased effectiveness of SICI and RI and improved writing in patients with writer's cramp. NMDYT1 had a normal response to cTBS300 over left PMd. We suggest that the reduced PMd to M1 interaction in dystonic patients is likely to be due to reduced excitability of PMd-M1 connections. The possible therapeutic effects of premotor rTMS may therefore involve indirect effects of PMd on SICI and RI, which this study has shown can be normalised by cTBS.

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Ying-Zu Huang: Research project conception and execution; statistic analysis design and execution; manuscript writing of the first draft. John C Rothwell: Research project conception; statistical analysis review and critique; manuscript review and critique. Chin-Song Lu: Research project conception; manuscript review and critique. JiunJie Wang: Research project organization; statistical analysis review and critique; manuscript review and critique. Rou-Shayn Chen: Research project conception and execution; statistical analysis review and critique; manuscript review and critique

The authors have no further financial disclosures to make.

Potential conflict of interest: Nothing to report.

Full Financial Disclosures of all Authors for the Past Year: Stock Ownership in medically-related fields: None. Consultancies: none. Advisory Boards: none. Partnerships: none. Honoraria: none. Grants: National Science Council of Taiwan (Huang YZ, Lu CS, Wang J, Chen RS) and Royal Society of the UK (Huang YZ and Rothwell JC). Intellectual Property Rights: none. Expert Testimony: none. Employment: Chang Gung Memorial Hospital and Chang Gung University (Huang YZ, Lu CS, Wang J, Chen RS), University College London (Rothwell JC). Contracts: none. Royalties: none. Other: none.

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Keywords

Premotor; rTMS; dystonia; theta burst; TBS

INTRODUCTION

A number of studies have claimed that inhibitory rTMS applied over the dorsal premotor cortex (PMd) can reduce symptoms of dystonia. Murase et al gave a single session of 0.2Hz rTMS to nine patients with writer's cramp and found an improvement in writing as well as increased duration of the cortical silent period.[1] Moreover, repeated days of 1Hz rTMS have been used by several groups and in all cases clinical improvements were reported.[2-5]

The rationale for targeting PMd with rTMS as a possible therapy in dystonia came from two sets of observations. First, PET studies showed that during movement, there was more activity in PMd compared with normal although activation of primary motor cortex (M1) was reduced.[6] Second, it was suggested that M1 was overexcitable in dystonia since MEP size increased more steeply with increasing background muscle force, or with increasing stimulus intensity, than in healthy subjects[7, 8] . With this background, it was reasoned that inhibitory rTMS over PMd would reduce overactivation of PMd whilst at the same time reducing excitability of M1 via inhibitory PMd-M1 interactions described in healthy subjects.[9]

A potential problem with this reasoning was recently highlighted by a double-pulse TMS study showing that the PMd-M1 connection is less excitable than normal in dystonia.[10] However, the measurements concerned interhemispheric rather than intrahemispheric PMd-M1connections, and were performed at rest rather than during movement. Moreover, the double-pulse paradigm only provides information about the excitability of the pathway, and this may not reflect levels of activity in the system, which is critical for their role in movement.

This study aimed to analyse how the motor system reacts to an inhibitory form of rTMS applied to PMd and how the rTMS affects writing in healthy subjects and in patients with focal hand dystonia. We also examined the response of DYT1 gene carriers, comparing the effect of PMd stimulation on individuals with dystonia (manifesting DYT1, or MDYT1) to those without symptoms of dystonia (non-manifesting DYT1, or NMDYT1). Although the experiments were mainly performed at rest, we believe that they give some insight into possible mechanisms whereby rTMS may affect motor control in dystonia patients, and enhance future therapeutic interventions.

METHODS

Subjects

Nine patients (5 men) with writer's cramp (WC), three genetically proven MDYT1 patients (3 men)[11] and five NMDYT1 subjects (3 men) ascertained by genetic and clinical assessment were recruited from the movement disorder clinics at the Chang Gung Memorial Hospital, Taiwan. Clinical details of the patients are given in Table 1. Nine healthy subjects (4 men) were recruited. The mean age of the WC group was 44.9±9.7 years, of the MDYT1 group was 36.3±9.5 years, of the NMDYT1 group was 42.6±13.8 years, and of the healthy controls was 42.7±12.1 years. Experiments in patients were performed after 24-hour drug withdrawal. All patients had clinical dystonia affecting the arm and hand studied. The dominant side was studied in healthy subjects. The experiments were approved by the Institutional Review Board and all subjects gave informed consent.

Electromyographic (EMG) recordings

EMGs were recorded from the first dorsal interosseous (FDI), flexor carpi radialis (FCR) and extensor digitorum communis muscles (EDC). Signals were sampled at 5kHz, amplified with a gain of 1000 and 5000 for FDI, 2500 for FCR and 5000 for EDC and filtered (3Hz to 2kHz). Trials in which the target muscle was not relaxed were rejected online.

Transcranial magnetic stimulation

Single pulse TMS was given using a 70mm figure-of-eight coil connected to a Magstim 200[2] (Magstim Co., UK), whereas theta burst stimulation (TBS)[12-14] was produced by a Magstim Rapid[2] Package through another 70mm figure-of-eight coil. The coil was placed tangentially to the scalp with the handle pointing backwards. The "motor hot-spot" was defined as the location where TMS produced the largest MEP from FDI. Active motor threshold (AMT) was defined as the minimum stimulation intensity over the "motor hot-spot" that could elicit an MEP of greater than 200μV in five out of ten trials during voluntary contraction of FDI.

Experimental procedure (figure 1)

cTBS300 (100 bursts) and cTBS600 (200 bursts of three 50Hz pulses at 5Hz given continuously) at an intensity of 80% AMT were applied over PMd (2.5cm anterior to the "motor hot-spot"). [9, 15] Sessions were performed on different days at least one week apart in a random order.

Premotor cTBS300 in healthy subjects and writer's cramp patients—The effect of cTBS300 applied over PMd (premotor TBS) on MEPs was evaluated using single pulse TMS given to the "motor hot-spot" at an intensity producing MEPs of about 1mV in control conditions. Thirty MEPs were recorded every 4.5-5.5s before cTBS300. After cTBS300, batches of MEPs to 12 single pulses were measured every 5 min for 30 minutes.

Motor and premotor cTBS300 in DYT1 gene carriers—The effect of premotor cTBS300 on MEPs was evaluated in NMDYT1 and MDYT1 groups. For comparison, we measured the effect of cTBS300 over M1 (motor TBS) in the same subjects.

Premotor cTBS600 in healthy subjects and writer's cramp patients—Two blocks of short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in FDI and one block of reciprocal inhibition (RI) in the forearm muscles were recorded before premotor cTBS600. Batches of MEPs to 12 single pulses were measured at 0, 5, 10, 15, 20 and 30 min after cTBS600. Between 20 and 30 min after cTBS600, one block of SICI/ICF and one block of RI were recorded.

SICI/ICF was tested using a paired-pulse technique[16] with the conditioning stimulus at 80% AMT and the test stimulus at the intensity producing an MEP of 1mV. Subjects received in a random order either the test stimulus alone, or conditioning-test stimuli at interstimulus intervals (ISIs) of 3, 7 and10ms for a total of eight trials per condition. The inter-trial interval was 4.5-5.5s. If necessary, we adjusted the test stimulus intensity while assessing SICI/ICF after premotor cTBS600 to maintain the amplitude of test MEPs at approximately 1mV.

To assess RI, the median nerve in the antecubital fossa was stimulated at an intensity eliciting half-maximal H-reflexes. The radial nerve was stimulated above the elbow at an intensity producing a response of 50uV in EDC. The third phase of RI was tested in this study since previous studies showed that only these intervals were significantly affected by premotor rTMS [15, 17]. We recorded H-reflex size during median nerve stimulation alone,

and for radial-medial stimuli at ISIs of 100 and 300ms. Stimuli were given every 5.4-6.6s in a random order for a total of eight trials per condition.

All the healthy subjects and seven of WC patients (4 men) participated in this session.

Effect of premotor cTBS600 on writing—Writing speed and Gibson Spiral Maze test[18, 19] were tested before and immediately after premotor cTBS600. For the writing speed test, subjects copied a page of Chinese as quickly as possible in 3 minutes and the number of characters copied was counted. In the Spiral Maze test, subjects traced the path in the maze from the centre outward with a pen. Errors were scored as the frequency with which the tracing touched any obstacles or the maze border. Subjects were instructed trace as quickly as possible and avoid errors if possible. All subjects practiced twice before assessment.

Data analysis

Differences in effects of TBS on peak-to-peak amplitude of MEP normalized to baseline between different subject groups or between different TBS stimulation paradigms were tested with two-way repeated measures ANOVA, while one-way ANOVA was used to asses the time course of effects. The third phase of RI was quantified as the average RI at ISI of 100 and 300ms. Paired t-tests were performed on SICI/ICF at ISI of 3, 7 and 10ms, the third phase of RI and writing tests to compare results before and after TBS. $P<0.05$ was considered statistically significant

RESULTS

Healthy subjects

Both cTBS300 and cTBS600 over PMd suppressed MEPs in healthy subjects (cTBS300: $F(7,56)=2.85$, $p=0.013$; cTBS600: $F(6,48)=5.49$, $p<0.001$) (Fig 2). ANOVA showed a significant effect of PULSE_NUMBER ($F(1,8)=6.28$, $p=0.037$) which post hoc t-tests (without correction) suggested was mainly because premotor cTBS600 produced stronger inhibition than premotor cTBS300 at 5 and 20 min ($p=0.021$ and $p=0.021$, respectively).

As previously reported with premotor cTBS300,[15] premotor cTBS600 reduced the third phase of RI ($t=-2.38$, $p=0.045$) (Fig 3A). In contrast although premotor cTBS300 does not change SICI/ICF,[15] premotor cTBS600 significantly reduced SICI at ISI of 3ms ($t=-3.56$, $p=0.007$), while the values at ISIs of 7 and 10ms remained unchanged ($p=0.306$ and $p=0.481$, respectively) (Fig 3A).

Writer's cramp

The effects of premotor cTBS300 and cTBS600 on MEPs in WC patients were significantly different from those in healthy subjects (cTBS300: GROUP × TIME interaction ($F(6,96)=2.66$, $p=0.020$) and GROUP effect ($F(1,16)=5.06$, $p=0.039$); cTBS600: GROUP effect ($F(1,14)=41.23$, $p<0.001$)) (Fig 2). This was because premotor cTBS300 and cTBS600 had no effect on MEPs in WC patients ($F(7,56)=1.19$, $p=0.322$ and $F(6,36)=0.56$, $p=0.761$, respectively).

Baseline RI and SICI were significantly reduced in WC patients (RI: $t=-3.61$, $p=0.003$; SICI: $t=-2.17$, $p=0.048$). In contrast to the results in healthy subjects, premotor cTBS600 in WC patients enhanced RI and SICI ($t=2.61$, $p=0.040$ and $t=2.61$, $p=0.040$, respectively). The values of SICI/ICF at ISI of 7 and 10ms remained unchanged by premotor cTBS600 ($p=0.287$ and $p=0.526$, respectively) (Fig 3B).

DYT1 gene carriers

Premotor cTBS300 significantly suppressed MEPs in NMDYT1 group ($F(7,28)=2.1$, $p=0.024$) as in healthy controls (GROUP: $F(1,12)=0.003$, $p=0.961$; GROUP × TIME interaction: $F(6,72)=0.38$, $p=0.888$). As in WC, premotor cTBS600 had no effect on MEPs (Fig 4A). In contrast, cTBS300 over M1, MEPs did not change MEPs in NMDYT1 ($F(7,28)=0.68$, $p=0.689$), while they were excessively suppressed in MDYT1. (Fig 4B) as previously reported.[20] Statistics were not performed on MDYT1 data because only 3 patients participated in this study.

Writing tests

Comparing WC and healthy subjects, there was a significant GROUP × TIME interaction and GROUP effect in writing speed ($F(1,14)=14.00$, $p=0.018$ and $F(1,14)=34.53$, $p<0.001$, respectively), significant GROUP × TIME interaction in speed of completion of the spiral maze ($F(1,14)=14.00$, $p=0.001$) and GROUP effect in the spiral maze error score ($F(1,14)=7.81$, $p=0.014$). The writing speed interaction was because premotor cTBS600 improved the writing speed in WC ($t=-3.231$, $p=0.018$), but not in healthy subjects ($t=0.67$, $p=0.523$). The interaction in speed of maze completion was because premotor cTBS600 slowed healthy subjects ($t=-3.701$, $p=0.006$) and tended to improve WC ($t=2.248$, $p=0.066$). The significant GROUP effects were due to the baseline differences between WC and healthy subjects.

DISCUSSION

The present results show that both cTBS300 and 600 over PMd suppress M1 in healthy subjects; in addition, cTBS600 reduces SICI and the third phase of forearm RI. cTBS to PMd had no effect on M1 excitability in dystonia patients, despite the fact that cTBS applied directly over M1 led to longer lasting after effects than in healthy controls (see also [20]). Nevertheless, cTBS600 to PMd increased SICI and RI bringing them back towards the normal range; it also improved writing speed and speed of maze completion even though it slowed the latter in healthy subjects. In NMDYT1 subjects the effect of premotor cTBS on M1 excitability was normal, despite the fact that they showed no effect of cTBS when applied directly to M1.

Effect of premotor TBS in healthy subjects

Conditioning stimuli applied to PMd can produce short latency effects on M1 excitability that are compatible with activation of a relatively direct PMd-M1 connection.[21]-[23] Although facilitation from PMd to contralateral M1 can be seen with conditioning intensities of 80% AMT,[23] ipsilateral effects appear to require higher intensities,[21] Thus we think that the effects of premotor cTBS on M1 excitability in this study are caused by changes in the inputs to ipsilateral connections rather than by their direct activation. The double-pulse work has not revealed any effects of left PMd stimulation on SICI tested at ISIs of 2-3ms, although subtle effects were seen at ISIs of 7-8ms after applying 1Hz rTMS.[24], [25] Thus, we speculate that the reduction in SICI caused by premotor cTBS600 is due to changes in activity of an indirect pathway that cannot be probed by the standard double-pulse method. Indeed, the fact that the shorter (20s versus 40s) trains of premotor cTBS300 did not produce any effect on SICI would be compatible with the idea that it may take some time to change tonic levels of activity in this pathway. Finally, as discussed in our previous paper,[15] the effect of premotor cTBS on the third phase of RI could be due to an interaction in the brainstem or spinal cord between descending inputs from PMd and afferents from peripheral nerve stimulation. The slowness in speed of completion of the maze after premotor cTBS600 was unexpected. We speculate that the virtual lesion created by cTBS600 disturbed the function of the normal brain to cause the slowness.

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Effect of premotor TBS in patients with dystonia

There was no effect of premotor cTBS on M1excitability in dystonia patients. This may relate to the reduced excitability of PMd-M1 connections in dystonia [10] as well as one previous observation:[26] In healthy subjects, 1Hz rTMS reduced metabolic activity in PMd and distant connected sites including sensorimotor cortex. In patients with hand dystonia, this effect was larger than normal in PMd, SMA and PMv, but not in the sensorimotor cortex. Perhaps the latter was isolated from the changes because of reduced PMd-M1 connectivity. The increased cortical reaction to rTMS coupled with decreased PMd-M1 connectivity would also be consistent with the fact that in contrast with the present results, cTBS directly over M1 has a larger effect on corticospinal excitability than normal.[20]

The effect of premotor cTBS600 on SICI and RI was opposite to that in healthy subjects and brought values towards the normal range in dystonia; it also improved writing performance. The effect on the third phase of RI parallels the result of a previous 1Hz rTMS study.[17] However, the SICI result was unexpected particularly since there was no effect on MEPs in the same patients. This suggests that premotor cTBS influences MEP excitability by a different pathway to its effect on SICI. If so, then this latter pathway may remain operational in dystonia. Why then is the effect on SICI opposite to normal? It could be that in the baseline state, tonic PMd input in healthy subjects increases the excitability of SICI whereas in dystonia it decreases SICI. If cTBS reduced this tonic effect it would decrease SICI in normals and increase it in dystonia.

Effect of premotor TBS in NMDYT1 individuals

In contrast to affected patients, NMDYT1 subjects had normal PMd-M1 interactions after cTBS. This implies that PMd-M1 connections and the response of PMd to cTBS were within normal limits. However, the finding that PMd reacts normally to cTBS was unexpected in view of the fact that the direct effect of cTBS over M1 is much smaller than normal in NMDYT1. Presumably a differential effect on plasticity in different cortical areas is part of the phenotypic expression of the DYT1 gene in these subjects. It would parallel the fact that motor cortical inhibition is reduced in NMDYT1 subjects whereas spinal circuits seem to be normal.[27] However, studies on more patients would be needed to confirm this.

Pathophysiology of dystonia

The present study and other recent work on PMd-M1 interactions indicate that there are changes in the excitability of inter-regional connections in dystonia. Which, if any, of these effects are primary and which secondary to the disease process is unknown. For example, reduced PMd-M1 interaction could compensate for increased PMd activity in dystonia; alternatively, the increased PMd activity could be compensating for reduced PMd-M1 connectivity. Abnormal connectivity could even be secondary to the dystonic posture.

Nevertheless, the current findings provide insight into therapeutic effects of premotor stimulation in dystonia. If PMd-M1 connectivity is reduced, then therapeutic effects of premotor rTMS as well as its normalisation of SICI and RI may not be via input to M1 but via indirect effects, on other cortical areas or even brainstem or spinal circuits. Premotor cortex may therefore lie closer to the primary mechanism of dystonia than M1.

In summary, the excitability of PMd-M1 interactions is impaired in patients with dystonia possibly due to dysfunction of premotor-motor connections. This could result in PMd overactivation seen in functional imaging studies. Alternatively the connection could be suppressed in response to an intrinsically hyperexcitable PMd. Normalisation of SICI and RI by rTMS over PMd may relate to possible therapeutic benefits.

Acknowledgments

Financial disclosure related to research covered in this article: This work was supported by the National Science Council of Taiwan (Contract Nos. NSC 94-2314-B-182A-057/ NSC 95-2314-B-182A-012/ NSC96-2314-B-182A-003), Chang Gung Memorial Hospital (Contract No. CMRPG34001) and Royal Society of the UK (UK-Taiwan Joint Project Grant).

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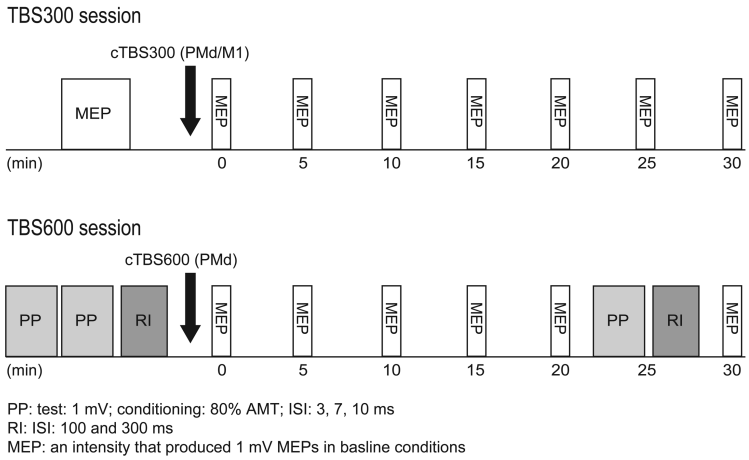

Fig 1. The diagram of experiment procedures

(A) cTBS300 sessions: cTBS300 was given to PMd or M1, and MEP size was assessed before and after cTBS300. (B) cTBS600 session: MEP size, SICI/ICF and RI was assessed before and after premotor cTBS600.

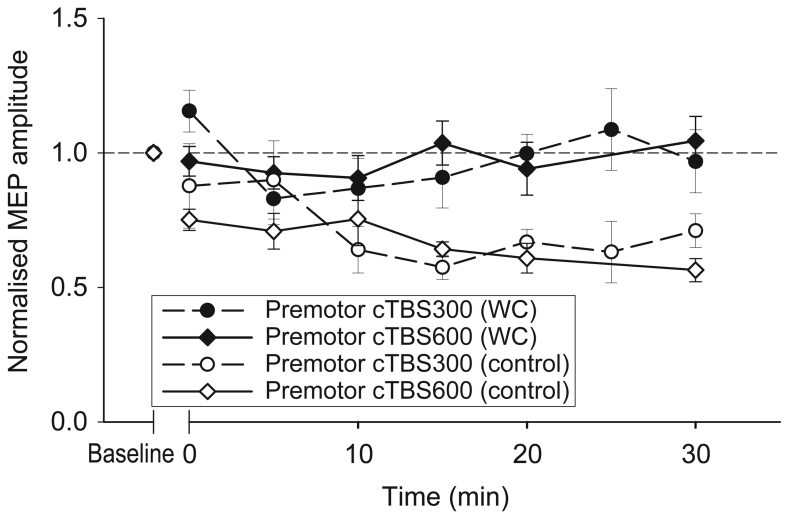

Fig 2. The effect of premotor cTBS300 and 600 on MEPs in healthy subjects and writer's cramp patients

Both premotor cTBS300 and 600 suppressed MEPs in healthy subjects (control). In contrast, neither premotor cTBS300 nor premotor cTBS600 changed the MEP size in patients with writer's cramp (WC). Error bars refer to the standard error of the measurements (SEM).

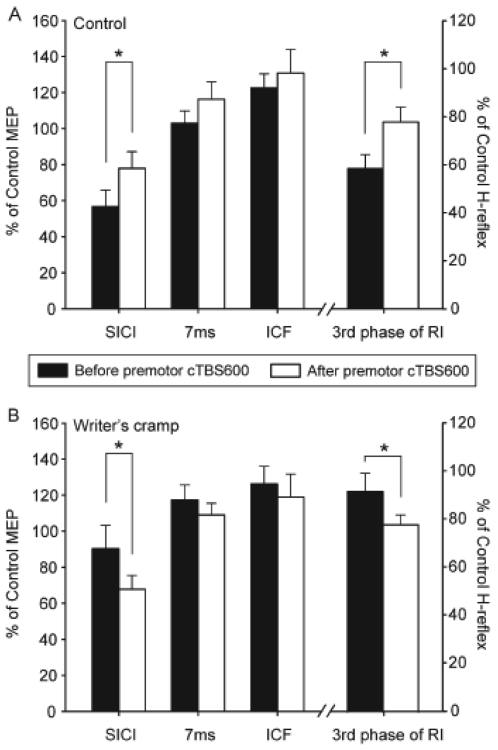

Fig 3. The effect of premotor cTBS600 on SICI/ICF and RI

SICI and RI were reduced in healthy subjects (control) (A), but enhanced in WC patients (B) following premotor cTBS600. ICF and the paired-pulse excitability at ISI of 7ms remained unchanged in both groups of subjects. Error bars refer to SEM.

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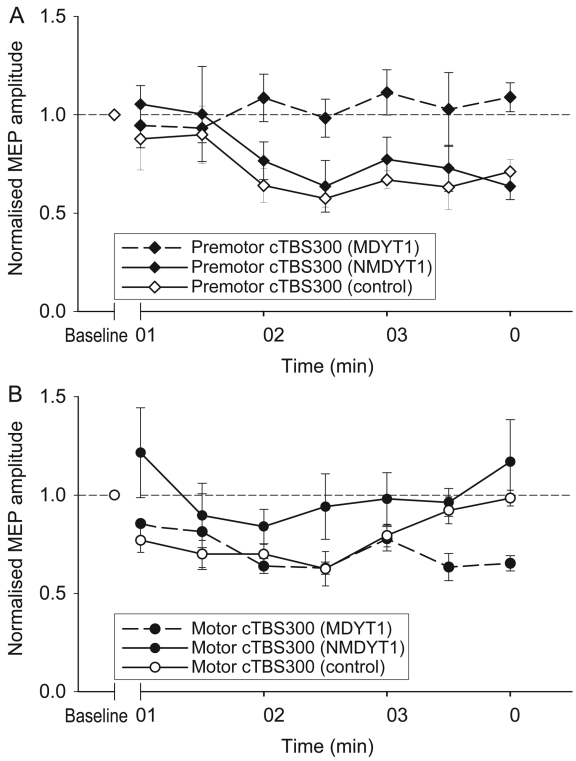

Fig 4. The effect of premotor and motor cTBS300 on MEPs in DYT1 gene carriers

(A) Premotor cTBS300 suppressed MEPs in NMDYT1 subjects as in healthy subjects, but had no effect on MEPs in MDYT1 subjects. (B) Motor cTBS300 produced excessive suppression on MEPs in MDYT1 subjects, but had no effect in NMDYT1 subjects.

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TABLE 1

Demographic data of patients with dystonia

No.	Age	Sex	Onset *	Clinical features	Drugs ever used
WC-1	54	M	47	Flexion of the fingers and wrist, ulnar deviation of the wrist, pain, tremulous writing[a]	Oxa, Tri, Clo, Bac, Cbz, BTX
WC-2	29	F	21	Flexion of the fingers and wrist, shoulder elevation, tremulous writing[a], pain	Tri., Clo, Cbz, BTX; Pro
WC-3	39	F	35	Flexion of the thumb, index and middle fingers, shoulder elevation, tremulous writing[a]	Tri, Clo, BTX, Bez
WC-4	57	F	44	Tightly holding the pen; flexion of the fingers and wrist; pronation of the wrist, pain	Cbz, Clo
WC-5	50	M	43	Difficulty in initiation of writing, flexion of the thumb, index fingers, nibs darting, pain	Tri, Cbz, Clo, BTX
WC-6	51	M	46	Difficulty in holding the pen w, flexion of the wrist; adduction of the elbow	Tri, Clo, Cbz, Bez
WC-7	45	M	27	Involuntary clenching and open the fist, extension and abduction of the elbow	Tri, Clo, Bez
WC-8	47	M	41	Extension with radial deviation of the wrist, supination of the elbow, tremulous writing[a]	Tri, Clo, Pri, BTX
WC-9	32	F	16	Flexion of thumb and index fingers, radial extension of the wrist and elbow	Tri, Clo, BTX
MDYT 1	27	M	9	Left foot focal dystonia Tri	
MDYT 1	46	M	11	Generalised dystonia	Tri, Clo, Bez, Bac
MDYT 1	36	M	28	Segmental dystonia involving neck and trunk	Tri, Clo, Cbz, BTX

Oxa, oxcarbazepine; Tri, trihexyphenidyl; Clo, clonazepam; Top, topiramate; Cbz, carbamazepine; Pro, propranolol; Bez, benzodiazepam; Bac, baclofen; Pri, primidone; BTX, botulinum toxin A injection. There is no use of botulinum toxin in the past 4 months.

*The age at onset of years.

[a]Denote the abnormal posture when writing showed jerky and tremulous dystonic movement.