Low and high-frequency repetitive transcranial magnetic stimulation for the treatment of spasticity

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The development of non-invasive techniques of cortical stimulation, such as transcranial magnetic stimulation (TMS), has opened new potential avenues for the treatment of neuropsychiatric diseases. We hypothesized that an increase in the activity in the motor cortex by cortical stimulation would increase its inhibitory influence on spinal excitability through the corticospinal tract and, thus, reduce the hyperactivity of the gamma and alpha neurons, improving spasticity. Seventeen participants (eight males, nine females; mean age 9y 1mo [SD 3y 2mo]) with cerebral palsy and spastic quadriplegia were randomized to receive sham, active 1Hz, or active 5Hz repetitive TMS of the primary motor cortex. Stimulation was applied for 5 consecutive days (90% of motor threshold). The results showed that there was a significant reduction of spasticity after 5Hz, but not sham or 1Hz, stimulation as indexed by the degree of passive movement; however this was not evident when using the Ashworth scale, although a trend for improvement was seen for elbow movement. The safety evaluation showed that stimulation with either 1Hz or 5Hz did not result in any adverse events as compared with sham stimulation. Results of this trial provide initial evidence to support further trials exploring the use of cortical stimulation in the treatment of spasticity.

See end of paper for list of abbreviations.

Spasticity is a common symptom in neurological disorders. One of the causes of spasticity is motor cortex damage that leads to a decrease in the cortical input to the corticospinal tract, resulting in a disinhibition of spinal, segmental excitability and an increase in the muscle tone.[1] This increase in muscle tone is marked by a velocity-dependent enhancement of the stretch reflex.[2–4]

The role of the motor cortex in the development of spasticity has been extensively demonstrated in primate studies. Specifically, ablation of Brodmann's area 4 in macaque monkeys results in persistent spasticity in addition to partial motor impairment,[5] and bilateral removal of Brodmann's areas 4, 6, and 8, as well as the posterior parietal cortex (area 7) in infant monkeys leads to development of spastic paraplegia.[6] In humans, patients undergoing surgery for intractable epilepsy revealed the development of spasticity in cases of extensive motor or premotor ablations.[7]

Cerebral palsy (CP) is a common cause of spasticity. CP results from a permanent static lesion of the cerebral motor cortex that occurs before, at, or within 2 years of birth.[8] The loss of descending inhibitory input through corticospinal tracts results in an increase in the excitability of gamma and alpha neurons, resulting in spasticity.[9] Spasticity is an important contributor to the quality of life of patients with CP as it leads to musculoskeletal complications such as contractures, pain, and subluxation.[10] Furthermore, the elimination of spasticity brings motor function improvement for these patients.[10] Although many therapies to reduce and control spasticity are available, they are associated with several disadvantages, such as elevated cost (e.g. botulinum toxin [BTX]), serious adverse events (e.g. BTX and intrathecal baclofen), and lack of efficacy (e.g. hyperbaric oxygen, gamma aminobutyric acid [GABA] agonists, muscle relaxants). Therefore, there is a pressing need for the development of new treatments.

Given the pathophysiology of spasticity, we hypothesized that an increase in the activity in the motor cortex of patients with CP would increase the inhibitory input to the corticospinal tract and reduce the hyperactivity of the gamma and alpha neurons.[1,11] Non-invasive focal modulation of the motor cortex was not possible until the advent of techniques of non-invasive brain stimulation, such as transcranial magnetic stimulation (TMS). TMS is based on a time-varying magnetic field[12] that generates an electric current inside the skull, where it can be focused and restricted to small brain areas depending on the coil geometry and shape.[12] It has been demonstrated that this current, if applied repetitively (rTMS), induces a cortical modulation that lasts beyond the time of stimulation.[12]

We therefore hypothesized that excitatory rTMS applied over the motor cortex would increase motor cortex activity and result in an increase in the inhibitory input through the corticospinal tract to the spinal cord, thus reducing alpha neuron hyperactivity and consequently clinical spasticity. Indeed, it has been shown that 5Hz rTMS of the primary motor cortex induces an overall increase in excitability of the corticospinal output system, including spinal motoneurons.[11,13] Therefore, in this study we sought to determine whether a 5-day course of 5Hz rTMS of the motor cortex as compared with 1Hz rTMS and sham rTMS would result in a reduction in spasticity in these patients and to determine the safety of rTMS in children with CP. Although rTMS has been extensively studied in adults, safety data on children are few, specifically regarding the use of high frequency rTMS as most of the TMS studies on children

have used single-pulse TMS only (see review[14]).

Method

PARTICIPANTS

Seventeen patients (mean age 9y 1mo [SD 3y 2mo]) participated in this study. Patients were prospectively and sequentially selected from a specialized rehabilitation center for children with CP if they fulfilled the following criteria: (1) diagnosis of CP according to clinical criteria;[15] (2) minimum age of 5 years old and maximum age of 18 years; (3) upper limb plasticity ≥1 according to Ashworth scale. Patients were excluded if they had: (1) any contraindications to rTMS;[16] (2) severe spasticity (defined as a score of 5 in the Ashworth scale) and contractures; and (3) uncontrollable epilepsy defined as the occurrence of seizures despite the use of at least one antiepileptic drug (AED) in adequate dose. All patients had spastic quadraplegia.

All patients continued their medications for epilepsy and spasticity as prescribed by their treating physician and medication changes were not allowed unless there was a strong clinical reason. This was not necessary in any of our patients. The general clinical characteristics are summarized in Table I.

This study was conducted at the University of Sao Paulo in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from the participants' parents prior to inclusion in the study.

EXPERIMENTAL DESIGN

This study was a randomized, double-blind, sham-controlled, parallel design clinical trial in which patients were randomized to receive five consecutive daily sessions of sham or active rTMS (1Hz or 5Hz). Patients and the investigators, except the investigators that applied rTMS, were blind to the treatment arm.

During the baseline period, patients were randomized in a 1:1:1 ratio to receive sham (six patients), 1Hz active (six patients), or 5Hz active (five patients) rTMS respectively. Randomization was performed using the order of entrance in the study and a randomization table previously generated by a computer using randomization blocks of six (for each six patients, two were randomized to each treatment) to minimize the risk of unbalanced group sizes.

TRANSCRANIAL MAGNETIC STIMULATION

Focal TMS of the motor cortex was performed with a figure-of-eight coil (outside diameter of each wing 7cm) and a Dantec stimulator (1.5 Tesla version; Medtronic, Minneapolis, USA). The motor threshold (MT) was defined as the lowest stimulus intensity required to elicit motor-evoked potentials of =0.05mV in the contralateral, resting abductor pollicis brevis muscle in at least five of 10 trials with the coil over the optimal scalp position.

The stimulation site was the site defined for the MT determination. Patients received five consecutive rTMS sessions from Monday to Friday applied in the morning (8am to 10am) using the following parameters: (1) Group 1 (1Hz stimulation): we applied the same number of pulses as the 5Hz condition (1500 pulses) and same intensity; however these pulses were applied in a continuous train; (2) Group 2 (5Hz stimulation): we used the same parameters used in the study of Quartarone et al.[13] Five 1-minute trains of 5Hz rTMS were applied with an interval of 2 minutes between the trains (total of 1500 pulses per session) and with an intensity of 90% of the motor threshold; and (3) Group 3 (sham stimulation): we used the same stimulation parameters (half received the 5Hz parameters and half the 1Hz parameters); however a specially-designed sham coil (Medtronic, Minneapolis, USA) was used.

We used the frequency of 5Hz and intensity of 90% of MT as it has been suggested by a recent study[13] that stimulation with these parameters can increase the inhibitory input to alpha motoneurons and frequency of 1Hz was used to compare whether the effects of rTMS on spasticity are specific for the frequency of stimulation.

ASSESSMENTS

To characterize the study population, a number of tests were performed at baseline by a blinded rater (see Tables I and II). Those tests were the Zancolli grade and House scores to quantify the degree of spasticity, and the Pediatric Evaluation of Disability Inventory (PEDI) to assess disability in daily life aspects.

The study endpoints were assessed at baseline and at the end of the treatment (after 5 days of stimulation) by a blinded rater. The posttreatment evaluation was performed 2 hours after the last session. The study endpoints were: (1) passive range of motion (ROM) of thumb adduction, wrist dorsal flexion and extension, and elbow dorsal flexion and extension. The maximum deviation in degrees was measured using a clinical goniometer; (2) the 5-point Ashworth scale was used to assess muscle tone around the fingers, wrist, and elbow joints; and (3) relative's report on social, emotional, and physical domains. We created an instrument to evaluate the impact of rTMS treatment in these domains. This instrument was composed of questions in which parents reported whether the patients were experienc-

Table I: Demographic information and spasticity and daily living characterization for each treatment group

	1Hz rTMS	*5Hz rTMS*	*Sham rTMS*
Age, y (SD)	9.8 (4.6)	9.8 (3.6)	8 (1.89)
Sex, M/F	4/2	2/3	2/4
Zancolli score 1[a]	4	3	6
Zancolli score 2[a]	2	0	0
Zancolli score 3[a]	0	2	0
House score 1[b]	4	3	3
House score 2[b]	1	2	2
House score 3[b]	1	0	0
PEDI Self-care (SD)	28.5 (22.1)	20 (21.8)	19.5 (8.1)
PEDI Mobility (SD)	13 (21.2)	12.5 (13.5)	7.8 (3.5)
PEDI Social func. (SD)	32.7 (24.2)	23.5 (20.1)	26.5 (15.1)

[a]Zancolli classification consists of a diagram of grip and release pattern in which a score of 1 indicates mild compromise of finger extension and a score of 3 indicates no active finger extension possible. [b]No patient presented House scores greater than 3. House scores indicate the degree of metacarpal deformity such that 1 indicates metacarpal adduction deformity; 2 indicates metacarpal adduction and flexion deformity; 3 indicates metacarpal adduction and hyperextension deformity with instability of the metacarpal joint; and 4 indicates metacarpal adduction and metacarpal and interphalangeal flexion deformity. The Pediatric Evaluation of Disability Inventory (PEDI) measures functional performance at home and in the community in the areas of functional skills, mobility, and social function. The scores vary according to the domains: self-care (0–73); mobility (0–59); and social function (0–65). Maximum scores indicate function within the range of population norms. rTMS, repetitive transcranial magnetic stimulation.

ing symptoms related to sleep, social behavior, mobility, and vegetative symptoms (such as salivation).

STATISTICAL ANALYSIS

Analyses were done with STATA statistical software version 8.0 (StataCorp, College Station, Texas, USA). Data input was performed by a blinded researcher (NBP) and checked by another researcher (FF). The primary outcomes of this study were spasticity change as measured by ROM and Ashworth scores. For ROM scores, we considered this variable as continuous and performed a repeated-measures analysis of variance (ANOVA), in which the ROM was the dependent variable and the covariates were time (baseline and posttreatment), group (1Hz, 5Hz, and sham), and the interaction term time versus group. If appropriate, post-hoc comparisons, corrected for multiple comparisons using Bonferroni correction, were carried out. For Ashworth scores, because this instrument is based on an ordinal scale, we performed a 3×1 table in which the row was the type of treatment (1Hz, 5Hz, sham) and the column was the difference in scores between baseline and after the stimulation. We used Fisher's exact test as a measure of association. For the secondary outcome (cognitive analysis), we performed a similar analysis, considering the difference between pre- and posttreatment in the different domains. To test for normality, we used the Skewness and Kurtosis coefficient. This test disclosed that our data were normally distributed. Data are reported as mean and standard deviation (SD). Statistical significance refers to a two-tailed p value <0.05.

Results

All patients were able to tolerate the TMS treatments, with no incidence of seizures. The three treatment groups did not differ with respect to age, sex, Zancolli and House scores, or PEDI scores (general items – self-care, mobility, and social function; see Table I).

Seizures in most of the patients were well controlled with AEDs (valproate, carbamazepine, benzodiazepine, phenobarbital, baclofen, and others). The number of patients taking each medication did not differ across the three groups, nor was there any difference in the average number of medications taken by patients in each group. The medications most commonly taken were valproate and benzodiazepine.

ASHWORTH SCORES

The effects of treatment group on Ashworth scores did not reach significance for any joint (Fisher's exact test, fingers: p=0.74, wrist: p=0.26, elbow: p=0.15). With respect to the elbow, three of five patients in the 5Hz group improved their scores in contrast to two of six patients in the 1Hz group and none of six patients in the sham group, suggesting a positive effect of the 5Hz rTMS treatment. As an exploratory analysis we compared elbow scores from the 5Hz group with the sham groups. While the difference between these groups did not reach statistical significance (χ^2=5.24, degrees of freedom [df]=2, p=0.073), the presence of a trend of improvement in the 5Hz treatment group is shown (see Table II).

RANGE OF MOTION SCORES

Two-way ANOVAs revealed significant interactions between group and time for each joint motion with the exception of thumb adduction, for which there was nevertheless an observed trend (Table III; thumb adduction: F=3.47, df=2,14, p=0.06; wrist flexion: F=5.47, df=2,14, p=0.018; wrist extension: F=29.15, df=2,14, p<0.001; elbow flexion: F=5.83, df=2,14, p=0.014; elbow extension: F=5.54, df=2,14, p=0.017). Post-hoc analyses (one-way ANOVAs with a Bonferroni correction) were carried out for each significant interaction.

For wrist flexion and extension scores as well as elbow flexion scores, there was no significant difference between pre- and post-treatment testing sessions in the 1Hz and sham groups

Table II: Number of patients in each group in each Ashworth category before and following treatment for fingers, wrist, and elbow

Fingers	*1Hz rTMS*			*5Hz rTMS*			*Sham rTMS*		
Ashworth scores	0	1	2	0	1	2	0	1	2
Pre-TMS, *n*	3	3	0	0	5	0	2	4	0
Post-TMS, *n*	4	1	1	2	3	0	2	3	1
Wrist	***1Hz rTMS***			***5Hz rTMS***			***Sham rTMS***		
Ashworth scores	0	1	2	3	0	1	2	3	0	1	2	3
Pre-TMS, *n*	1	3	2	0	0	2	3	0	1	4	1	0
Post-TMS, *n*	3	2	0	1	1	4	0	0	0	5	1	0
Elbow	***1Hz rTMS***				***5Hz rTMS***				***Sham rTMS***			
Ashworth scores	0	1	2	3	0	1	2	3	0	1	2	3
Pre-TMS, *n*	1	2	3	0	0	1	2	2	0	2	4	0
Post-TMS, *n*	2	1	3	0	0	2	3	0	0	1	5	0

The 5-point Ashworth scale was used to assess muscle tone around fingers, wrist, and elbow joints. Scores range from 0 to 4, with 0 indicating no increase in muscle tone and 4 indicating that the affected part is rigid in flexion or extension. TMS, transcranial magnetic stimulation.

(wrist flexion: p=0.63 and 1 respectively; wrist extension: p=0.83 and 0.83 respectively; elbow flexion: p=0.66 and 1 respectively). All three of these measurements, however, showed significant improvement for the 5Hz group (wrist flexion: p=0.023, mean difference of –10° [95% confidence interval {CI} 9.4–10.6] or –11.4%; wrist extension: p=0.004, mean difference of –27° [95% CI 18.5–35.5] or -48.2%; elbow flexion: p=0.033, mean difference of –14° [95% CI 9.2–18.8] or –20.6%). For elbow extension scores, although the one-way ANOVA showed a significant result, there was no significant difference between testing sessions in any of the three groups (p=0.72, 0.55, and 0.73 for the 1Hz, 5Hz, and sham groups, respectively).

SUBJECTIVE REPORT

Table IV shows the scores of the subjective evaluation divided into the groups of treatment. There was no significant difference in any of these domains across the groups of stimulation, showing that stimulation was not harmful for subjective behavior and some aspects of daily living.

Discussion

Our study shows that 5Hz rTMS might exert a beneficial role in spasticity in patients with CP. The effects seem to be modest and were not significant in all the joints and tests performed. Another important result of this trial is that high-frequency rTMS delivered to pediatric patients with epilepsy with adequate control of their seizures did not induce seizures. Finally, rTMS – with either low or high frequency – did not result in any adverse effects, as spontaneously reported, and also assessed by several domains in the subjective evaluation as compared to sham stimulation.

This study was based on previous work showing that subthreshold 5Hz rTMS induces an overall increase in the corticospinal excitability including an increase in the excitability of the spinal cord, as shown by direct stimulation of the spinal cord with electrical stimulation,[13] and extends findings in adults on the effects of modulation of corticospinal excitability on segmental spinal excitability.[1,11] Based on these findings, we hypothesized that this increase in the spinal cord excitability could restore the inhibition to the spinal motoneurons and, therefore, reduce clinical spasticity. Although we showed a significant effect on some of the tests, the effect was modest. One factor that supports the potential benefits of rTMS is that the effects were specific to the frequency of stimulation, with 5Hz rTMS resulting in the largest effect. Some factors that might have contributed to the small magnitude of this effect were the small sample size of this study; the low baseline degree of spasticity in these patients compared with spasticity found in other neurological disorders such as multiple sclerosis and spinal cord injury; and the dose of rTMS that might not have been enough as more sessions of rTMS might be necessary to induce a clinical meaningful result. For other conditions, for instance depression, five consecutive sessions do not result in a consistent or sustained mood improvement; however, when the number of sessions is increased to 10 or 15, the clinical antidepressant effects become evident (see meta-analysis[17]).

The pathophysiology of spasticity in CP has been extensively studied. Injury to cortical motoneurons decreases the inhibitory input to the reticulospinal and corticospinal tract,

Table III: Mean (SD) difference (in degrees) between post- and pre-treatment (post- minus pre-) range of motion scores

	1Hz rTMS	*5Hz rTMS*	*Sham rTMS*	*p value*
Thumb adduction	19.17 (5.5)	32 (16.4)	8.33 (14.7)	0.060
Wrist flexion	5 (5.5)	10 (0.7)	0 (6.3)	0.018
Wrist extension	2.5 (4.2)	27 (9.7)	–0.83 (4.9)	<0.001
Elbow flexion	–2.5 (7.6)	14 (5.5)	0 (11.0)	0.014
Elbow extension	–0.83 (2.0)	8 (8.4)	–1.67 (4.1)	0.017

Note that a negative difference means a decrease (worsening) in the degree of motion.
TMS, transcranial magnetic stimulation.

Table IV: Subjective evaluation

		1 Hz rTMS	*2 Hz rTMS*	*Sham rTMS*	*p value*
Sleep	Improvement (2 items)	2	2	3	0.56
	Worsening (2 items)	0	0	1	
Social function	Improvement (6 items)	7	6	5	0.32
	Worsening (7 items)	0	0	1	
Mobility	Improvement (4 items)	7	7	10	0.33
	Worsening (4 items)	1	0	0	
Vegetative symptoms	Improvement (1 items)	1	0	0	0.22
	Worsening (items)	0	1	1	

If a patient has one of the items, this patient gets the score 1. In this table, the sum of items for all the patients in each group is then summarized. Therefore the maximum score for each group is equal to the number of patients in each group times the number of items. TMS, transcranial magnetic stimulation.

therefore producing an increase in the excitability of gamma and alpha neurons, leading to spasticity. The use of cortical stimulation is an attempt to increase the inhibitory input from motor cortical neurons. Indeed, this population of patients would be particularly suitable for this treatment as the loss of cortical motoneurons is not complete, therefore leaving the possibility of modulating the corticospinal system. There are few reports of the use of cortical stimulation for the treatment of spasticity. A study performed 30 years ago showed that electrical stimulation of the cerebellum in monkeys could significantly reduce surgically-induced spasticity.[18]

There are several options to treat spasticity in CP, such as BTX, oral pharmacological agents, neuromuscular blocking agents, orthotics, and physiotherapy (see review[19]). However, although some of these interventions are effective, they are also associated with adverse effects and local discomfort, e.g. BTX. The advantage of rTMS in this scenario is that this therapy is non-invasive, practically painless, and, in fact, well tolerated by children as shown by our study.

Despite the fact that rTMS has been shown to be safe for use in adults, there is little data regarding the safety of rTMS in children. A recent study performed by Quintana[14] reviewed 24 studies that involved 1034 children with an age range between 2 months and 18 years. Although this review showed that a large number of children had been studied with TMS, only seven studies were identified where rTMS had been applied (total of 34 children studied). In most of these studies, children with epilepsy were studied, therefore, only low-frequency rTMS was used.

Because one potential application for rTMS in children is for psychiatric symptoms, especially because recent data suggest that antidepressants might increase the risk of suicidal attempts in this population,[20] safety data of high-frequency rTMS in children are critical. In this study, although the main aim was not safety, we did show that high-frequency rTMS is not associated with adverse effects when compared with sham rTMS.

This study has some limitations. First, our subjective instrument to measure changes in some domains, such as social, emotional, and physical well-being, has not been validated before and, therefore, the results that stem from this test should be interpreted with caution and viewed as exploratory. Second, we did not perform a long-lasting evaluation and, therefore, cannot rule out that the effects of 5 days of rTMS might be quite transient. Further studies should evaluate the long-term effects of rTMS therapy on spasticity. Finally, this study has a small sample size and, therefore, it might have been underpowered for some of the analyses. Indeed the small sample size, together with Bonferroni correction, might have contributed to the lack of statistical significance in some of the analyses.

Although the results of our study did not show a clear effect of rTMS in reducing spasticity, our findings encourage further exploration of cortical stimulation – with rTMS or other techniques of non-invasive brain stimulation (transcranial DC stimulation) or even invasive techniques (epidural stimulation) in animals – for the treatment of spasticity. Due to our suggestive findings that high-frequency rTMS might be beneficial in reducing spasticity in children with CP, further larger randomized clinical trials seem warranted.

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References

1. Valero-Cabre A, Pascual-Leone A. (2005) Impact of TMS on the primary motor cortex and associated spinal systems. *IEEE Eng Med Biol* **24:** 29–35.
2. Noth J. (1991) Trends in the pathophysiology and pharmacotherapy of spasticity. *J Neurol* **238:** 131–139.
3. Young RR. (1994) Spasticity: a review. *Neurology* **44** (Suppl 9)**:** S12–20.
4. Gracies JM. (2005) Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. *Muscle Nerve* **31:** 535–551.
5. Hines M. (1936) The anterior border of the monkey's (Macaca mulatto) motor cortex and the production of spasticity. *Am J Physiol* **116:** 76.
6. Denny-Brown D, Yanagisawa N. (1971) The evolution of spastic paraplegia following cortical ablation in infant monkeys. *Trans Am Neurol Assoc* **96:** 169–172.
7. Laplane D, Talairach J, Meininger V, Bancaud J, Bouchareine A. (1977) Motor consequences of motor area ablations in man. *J Neurol Sci* **31:** 29–49.
8. Dabney KW, Lipton GE, Miller F. (1997) Cerebral palsy. *Curr Opin Pediatr* **9:** 81–88.
9. Goldstein EM. (2001) Spasticity management: an overview. *J Child Neurol* **16:** 16–23.
10. Flett PJ. (2003) Rehabilitation of spasticity and related problems in childhood cerebral palsy. *J Paediatr Child Health* **39:** 6–14.
11. Valero-Cabre A, Oliveri M, Gangitano M, Pascual-Leone A. (2001) Modulation of spinal cord excitability by subthreshold repetitive transcranial magnetic stimulation of the primary motor cortex in humans. *Neuroreport* **12:** 3845–3848.
12. Pascual-Leone A, Bartres-Faz D, Keenan JP. (1999) Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. *Philos Trans R Soc Lond B Biol Sci* **354:** 1229–1238.
13. Quartarone A, Bagnato S, Rizzo V, Morgante F, Sant'angelo A, Battaglia F, Messina C, Siebner HR, Girlanda P. (2005) Distinct changes in cortical and spinal excitability following high-frequency repetitive TMS to the human motor cortex. *Exp Brain Res* **161:** 114–124.
14. Quintana H. (2005) Transcranial magnetic stimulation in persons younger than the age of 18. *J ECT* **21:** 88–95.
15. Levine MS. (1980) Cerebral palsy diagnosis in children over age 1 year: standard criteria. *Arch Phys Med Rehabil* **61:** 385–389.
16. Wassermann EM. (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol* **108:** 1–16.
17. Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. (2003) Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *Br J Psychiatry* **182:** 480–491.
18. Hemmy DC, Larson SJ, Sances A Jr, Millar EA. (1977) The effect of cerebellar stimulation on focal seizure activity and spasticity in monkeys. *J Neurosurg* **46:** 648–653.
19. Koman LA, Smith BP, Shilt JS. (2004) Cerebral palsy. *Lancet* **363:** 1619–1631.
20. Hammad TA, Laughren T, Racoosin J. (2006) Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* **63:** 332–339.

List of abbreviations

AED	Antiepileptic drug
MAS	Modified Ashworth Scale
MT	Motor threshold
PEDI	Pediatric Evaluation of Disability Inventory
ROM	Range of motion
rTMS	Repetitive transcranial magnetic stimulation
TMS	Transcranial magnetic stimulation