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CLINICAL NOTE

Noninvasive and Painless Magnetic Stimulation of Nerves Improved Brain Motor Function and Mobility in a Cerebral Palsy Case

Véronique H. Flamand, OT, MSc,[a,b] Cyril Schneider, PhD[a,c]

From the [a]Neuroscience Division, CHU de Québec Research Center, Québec, QC; [b]Faculty of Medicine, Université Laval, Québec, QC; and [c]Department of Rehabilitation, Faculty of Medicine, Université Laval, Québec, QC, Canada.

Abstract

Motor deficits in cerebral palsy disturb functional independence. This study tested whether noninvasive and painless repetitive peripheral magnetic stimulation could improve motor function in a 7-year-old boy with spastic hemiparetic cerebral palsy. Stimulation was applied over different nerves of the lower limbs for 5 sessions. We measured the concurrent aftereffects of this intervention on ankle motor control, gait (walking velocity, stride length, cadence, cycle duration), and function of brain motor pathways. We observed a decrease of ankle plantar flexors resistance to stretch, an increase of active dorsiflexion range of movement, and improvements of corticospinal control of ankle dorsiflexors. Joint mobility changes were still present 15 days after the end of stimulation, when all gait parameters were also improved. Resistance to stretch was still lower than prestimulation values 45 days after the end of stimulation. This case illustrates the sustained effects of repetitive peripheral magnetic stimulation on brain plasticity, motor function, and gait. It suggests a potential impact for physical rehabilitation in cerebral palsy.

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Muscle spasticity is a consequence of brain damage that is characterized by a velocity-dependent increase of muscle tone and hyperexcitability of the stretch reflex.[1] Among other disturbances found in children with cerebral palsy (CP), spasticity is a major cause of movement limitation and disruption of motor performance.[2] It therefore affects functional achievement of daily activities and participation in recreational activities.[3]

Noninvasive and painless magnetic stimulation of nerves/muscles, referred to as repetitive peripheral magnetic stimulation (rPMS), is an emerging approach already tested in adult neurologic populations to reduce spasticity[4-10] and improve performance in various motor[4-6,8,11] and perceptual-cognitive tasks.[6,12,13] It is proposed that the therapeutic effects of rPMS are based on the massive induced proprioceptive inflow that nurtures the central nervous system. Precisely, proprioceptive information generated by rPMS would not only modulate the excitability of specific spinal circuits[9] but also influence the synaptic mechanisms of brain plasticity involved in motor learning.[5,10] This is deemed to drive up neural excitability in the parietal areas and primary motor cortex (M1) and balance interactions between hemispheres, all contributing to the improvement of function.[5,7,9,12-14] Our recent study in children with CP[15] reported that the repetition of rPMS sessions could induce a significant reduction of the resistance of spastic plantar flexor muscles to stretch. Therefore, the present case study investigated the underlying mechanisms of 5 rPMS sessions on brain and function in CP. Clinical and corticomotor improvements and the impacts on gait performance are reported.

Case description

A boy with spastic hemiparetic CP aged 7 years 9 months was enrolled in 5 rPMS sessions with parents' written informed consent under ethical approval. He had suffered pre- or perinatal stroke of the left hemisphere (ischemic lesion of the corona radiata and a small subependymal hemorrhage). He was classified at level 1 on the Gross Motor Function Classification System, with no recent (<12mo) botulinum toxin injection in the plantar flexor muscles or recent (<1mo) change in medication and no active

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rehabilitation during the study. A baseline evaluation (on a Tuesday) and 5 rPMS sessions (sessions 1−5, each successive Thursday and Tuesday) were conducted over 3 weeks. Two follow-up sessions were ensured at 15 and 45 days after session 5. Clinical measures of the paretic lower limb were collected pre- and post-rPMS at sessions 1, 3, and 5 and at both follow-ups. A functional videographic gait test[16] was conducted at baseline, pre-rPMS in session 3, post-rPMS in session 5, and at both follow-ups. Corticomotor function was tested using transcranial magnetic stimulation (TMS) of the lesioned M1 at pre-rPMS in session 1 and post-rPMS in session 5.

Clinical testing by the same physical therapist and systematic assistance by the same occupational therapist for the whole study was ensured. Ankle ranges of active (volitional) and passive (manually imposed) dorsiflexion motion were measured using a handheld inclinometer maintained against a plastic plate on the forefoot to ensure reliable positioning. The participant was in a supine position with the hip and knee in full extension. Two measures were collected for each motion (active, passive). In case of a variation exceeding 5°, a third supplementary trial was performed, and the 2 closest measures were averaged. The resistance of plantar flexors to stretch was measured using a handheld dynamometer[a] positioned on the forefoot beneath the distal ends of the metatarsal bones. Stretch was initiated from the ankle's resting position by the physical therapist, who controlled the velocity of the passive dorsiflexion by counting silently "one-thousand-one." The total movement lasted 1 second and was performed at 60°/s to 75°/s. This method was acknowledged as a reliable intertrial measurement of resistive force[17] in the absence of a motor-driven system. The participant was seated on the treatment table, with his back resting on a removable backrest and his hips and knees at 90° and 30°, respectively, to avoid excessive stretch of muscles. Three measures were collected. In case of a variation >10%, a fourth supplementary trial was performed, and the 3 closest measures were averaged.

The videographic gait test[16] was conducted in a gymnasium on a 9-m walkway graduated with colored tape to facilitate the post-hoc calculation of walking parameters. The participant was asked to walk barefoot, at free speed, 6 times back and forth on the 9-m walkway (more methodologic details can be found in Drouin et al[16]). The videotapes of walking performance were analyzed by the same occupational therapist blinded to the time of recordings.

TMS has enabled safe and painless noninvasive investigation of the lesioned M1 and central motor pathways.[18,19] This technique uses a wire coil placed over the scalp to generate a local transient magnetic field that creates an electrical current in the brain. This electrical current flows through the targeted area and activates brain cells. When applied over the M1, TMS induces depolarization of corticospinal cells and produces a motor-evoked potential (MEP) recorded in muscles of the contralateral hemibody by surface electromyography. It therefore allows the testing of motor system maturation in children[20] with negligible risks following safety guidelines.[21]

TMS testing was conducted with the participant comfortably seated in a reclining and adjustable chair with legs and arms supported and knees flexed at 20°. Magnetic stimuli were applied using a 70-mm double-cone coil (connected to 2 Magstim 200^2 monophasic stimulators[b] and BiStim^2 module[b]) positioned over the M1 hotspot for the tibialis anterior (TA).[22] The hotspot was first approximated at 1.5 to 2cm lateral from the central vertex based on the International 10-20 System of electrode placement[23] and adjusted for evoking TA MEPs at the lowest stimulus intensity. The scalp was marked with a chirurgical pen to provide a visual reference for reliable positioning and orientation of the coil over the M1. The active motor threshold (AMT) refers to the lowest TMS intensity required to evoke MEPs in the target muscle and appears to be an index of cortical motor excitability.[18] Precisely, in the paretic TA of the 8-year-old participant, it was not possible to get MEP amplitudes of 100μV and was therefore not possible to follow the usual procedure to assess the AMT.[21] Therefore, the AMT of the paretic TA was the intensity required for eliciting at least 5 MEPs of amplitudes higher than the electromyographic background out of 10 trials.

At suprathreshold intensities of TMS, the amplitude and latency of MEPs are used to measure cortical motor function. The amplitude reflects the volume of M1 cells synchronized by TMS and the strength of corticospinal projections. The latency informs on corticospinal conduction time and indirectly informs on the synchronous arrival of descending volleys for depolarization of spinal motor neurons.[24,25]

Six to 10 MEPs at TMS intensity of 120% AMT were recorded. The paretic TA was activated at 15% of the maximal voluntary contraction (MVC) to stabilize motoneuronal excitability and spinal cord output.[25] MVC was determined by the mean background activity recorded during 3 trials of maximal isometric contraction of ankle dorsiflexors. Electromyographic recordings were collected using surface parallel-bar electromyographic sensors positioned with adhesive skin interfaces over the TA belly and a ground electrode on the patella (16-channel Bagnoli Desktop EMG System[c]). Signals were bandpass filtered (20−500Hz), amplified before digitization (2kHz), and stored for off-line analysis (PowerLab acquisition system[d]). Real-time TA activity was displayed online, and trials falling outside the stringent window of electromyographic level acceptance implemented in our software were rejected (15%±5% MVC). Auditory feedback was provided to help the child maintain 15% MVC of his paretic TA.

The rPMS protocol was strictly repeated at each of the 5 sessions. The rPMS was applied using a theta mode over the sciatic and tibial nerves (centrally on the back of the thigh and centrally in the popliteal fossa, respectively) and the common peroneal nerve (directly posterior to the head of the fibula). Theta mode consisted of 3 pulses at 50Hz, which were repeated every 200ms (5Hz)[26] and delivered by a Magstim Air Film Coil[b] (figure-of-8, biphasic waveform) connected to a high-frequency magnetic Magstim Rapid^2 Stimulator.[b] Stimulation intensity was set to produce palpable muscle contractions and ankle movements. Continuous theta-burst stimulation was used over the nerves of spastic hamstrings (180-s train of uninterrupted pulses over the sciatic nerve) and ankle plantar flexors (triceps surae, 60-s train of uninterrupted pulses over the tibial nerve). Intermittent theta-burst stimulation was then applied to elicit cyclic activation-relaxation

List of abbreviations:

AMT	**active motor threshold**
CP	**cerebral palsy**
MEP	**motor-evoked potential**
MVC	**maximal voluntary contraction**
M1	**primary motor cortex**
PNS	**peripheral nerve stimulation**
rPMS	**repetitive peripheral magnetic stimulation**
TA	**tibialis anterior**
TMS	**transcranial magnetic stimulation**

of dorsiflexors and repeated movements of ankle dorsiflexion (2-s trains of pulses repeated every 10s during 300s over the common peroneal nerve). The coil was held tangentially to the skin over the nerve spot with the long axis of its junction parallel to the nerve; this orientation is the most effective for activating nerve fibers.[10,27] Nerve spots were marked on the skin with a surgical pen to ensure reliable rPMS coil positioning throughout the 5 sessions. The subject was comfortably installed in a supine position during rPMS application. One advantage of this approach in children is the fun associated with the painless rPMS-induced contractions of muscles and associated movement.[15]

The study focused on 3 clinical outcomes (active ankle dorsiflexion, passive ankle dorsiflexion, resistance of plantar flexors to stretch) and 4 gait parameters (velocity, stride length, cadence, cycle duration). Three TMS outcomes of the paretic TA muscle were also analyzed: AMT (expressed in percentage of maximal stimulator output), mean MEP latency (ms), and mean peak-to-peak MEP amplitude (μV). Data are presented with descriptive statistics (means, SDs), raw differences in the mean values across trials, and percentage change relative to pre-rPMS values from session 1.

Figure 1 (left side) shows that active ankle dorsiflexion increased in session 1 after rPMS (7.0°±1.4°) compared with pre-rPMS (1.5°±0.7°), still increased after rPMS in session 3 (8.5°±0.7°), and reached its highest value at pre-rPMS in session 5 (15.5°±0.7°). Passive ankle dorsiflexion increased slightly in sessions 1 and 3 (29.0°±1.4° to 33.0°±1.4°) and then reached its highest value at pre-rPMS in session 5 (41.0°±1.4°), which represented a 41.4% increase when compared with pre-rPMS in session 1 (29.0°±1.4°). These changes of active and passive ranges of movement persisted at follow-up 1 (12.0°±1.4° and 40.5°±0.7°, respectively) and returned toward the pre-rPMS values of session 1 at follow-up 2 (4.5°±2.1° and 34.0°±2.8°, respectively). The right side of figure 1 shows that the resistance of the plantar flexors to stretch decreased at each time of measurement with the most important pre/post (acute) reductions (1.27 and 1.17kg) at sessions 1 and 3 (19.6% and 19.5% change, respectively). The resistance to stretch remained lower than pre-rPMS in session 1 (6.47±.15kg) at follow-ups 1 and 2 (4.93±.06kg and 5.67±.32kg, respectively, ie, 23.8% and 12.4% lower than pre-rPMS in session 1, respectively).

All gait parameters tested were improved (table 1). Walking velocity increased progressively over the sessions compared with pre-rPMS in session 1 (91.3±1.0cm/s), with differences at pre-rPMS in session 3 (98.0±6.3cm/s), post-rPMS in session 5 (103.0±5.9cm/s), and follow-up 1 (107.4±2.2cm/s). Stride length was longer at post-rPMS in session 5 (98.9±3.6cm) and follow-up 1 (99.5±7.5 cm) compared with pre-rPMS in session 1 (91.3±1.0cm). Cadence was faster (130.0±7.8 steps/min) and cycle duration was shorter (.93±.06s) at follow-up 1 compared with pre-rPMS in session 1 (120.0±0 steps/min; 1.00±0s, respectively). All gait parameters were equal or very similar to baseline at follow-up 2.

Figure 2 shows that the mean peak-to-peak TA MEP amplitude increased from pre-rPMS in session 1 (33.28±26.09μV) to post-rPMS in session 5 (74.81±19.17μV; 124.8% change). The mean

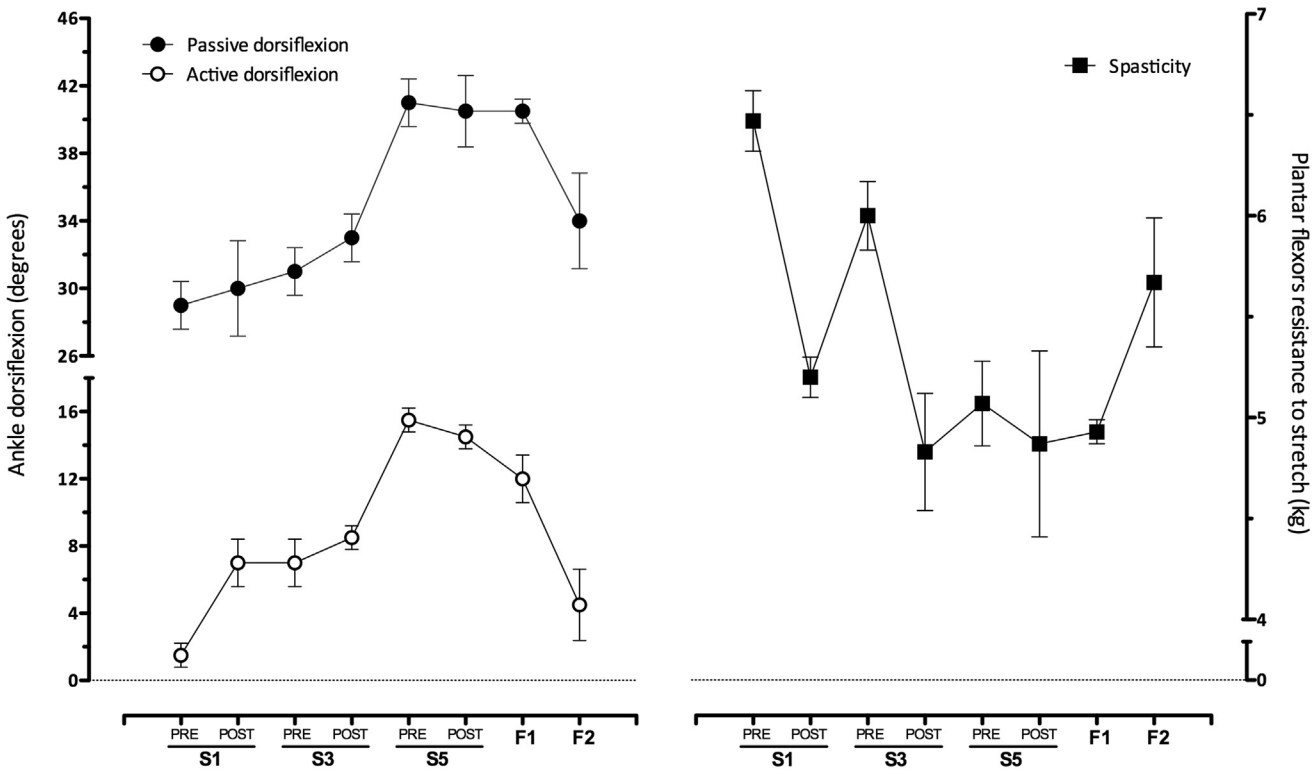

Fig 1 Clinical outcomes of the paretic ankle: concurrent dorsiflexion increase and spasticity decrease. Mean values ± SD at S1, S3, and S5 (pre- and post-rPMS) and F1 and F2. Left panel: passive and active dorsiflexion in degrees. Right panel: plantar flexors resistance to stretch. Abbreviations: S1, session 1; S3, session 3; S5, session 5; F1, follow-up 1 (15d after last session of stimulation); F2, follow-up 2 (45d after last session of stimulation).

Table 1 Gait outcomes

	Time of Measurement				
Gait Parameters	BL	Pre-S3	Post-S5	F1	F2
Walking velocity (cm/s)	91.3±1	98.0±6.3	103.0±5.9	107.4±2.2	92.7±2.2
Stride length (cm)	91.3±1	92.2±2.8	98.9±3.6	99.5±7.5	92.7±2.2
Cadence (steps/min)	120.0±0	127.5±8.2	125.0±7.8	130.0±7.8	120.0±0
Cycle duration (s)	1.00±0	0.94±0.06	0.96±0.06	0.93±0.06	1.00±0

Abbreviations: BL, baseline; F1, follow-up 1; F2, follow-up 2; Pre-S3, pre-rPMS of session 3; Post-S5, post-rPMS of session 5.

duration of MEP latency decreased from pre-rPMS in session 1 (31.25±1.17ms) to post-rPMS in session 5 (26.7±.67ms; 14.6% change). The AMT was not influenced.

Discussion

Our study showed an improvement of ankle function and gait in a 7-year-old child with spastic hemiparetic CP after 5 rPMS sessions concomitantly with changes of corticospinal function. These original results lead to new hypotheses on how rPMS in CP can influence brain plasticity and contribute to physical rehabilitation.

In CP, the exaggerated resistance of plantar flexors to stretch (spasticity), limitations of muscle strength and motor coordination, and lack of selective motor control all contribute to the reduced range of ankle dorsiflexion movement and impaired ankle function.[28-30] This reduction of ankle dorsiflexion amplitude in children with CP was especially related to the severity of plantar flexors spasticity.[31] In our study, concomitant improvements of both aspects suggest that rPMS has decreased resistance to ankle dorsiflexion (spastic plantar flexors tone reduction) and eased voluntary movement. Such effects of rPMS have already been proposed in adults with chronic stroke.[4,5,32] Our results showed more precisely not only that resistance of plantar flexors to stretch decreased at each time of measurement after rPMS application but also that this reduction persisted from one session to another and remained 45 days after the end of stimulation. This suggests the existence of intertwined acute and long-lasting aftereffects of rPMS on spastic tone in CP, which is in line with our previous study,[15] studies in spastic adults,[4-10] and a recent single-session study of children with CP.[33]

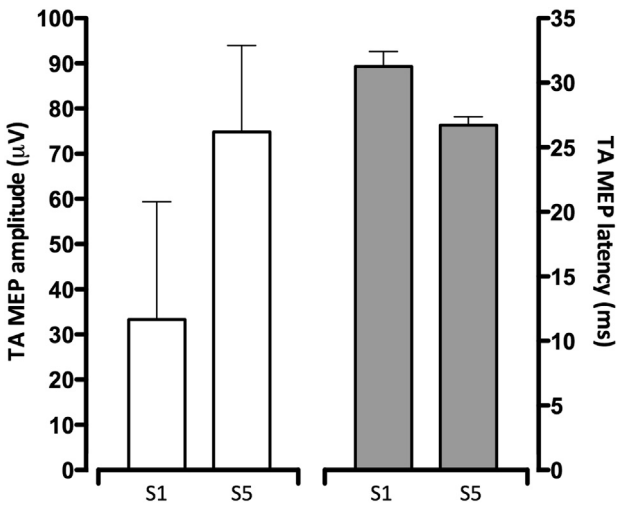

Fig 2 TMS outcomes of the paretic TA: concurrent increase of MEP amplitude and decrease of latency. Mean values ± SD at session 1 (S1, pre-rPMS) and session 5 (S5, post-rPMS). White bars indicate peak-to-peak amplitude of MEPs; gray bars, MEP latencies.

Interesting changes of TMS outcomes were observed along with ankle function improvements after rPMS. The increase of MEP amplitude and decrease of MEP latency in our case study could be consonant with an influence of rPMS on the M1 circuits involved in ankle motor control.[24,25] Indeed, on the one hand, rPMS was shown to influence the activation of frontoparietal networks involved in motor programming,[4,5] and on the other hand, TMS measures of corticomotor excitability for a single subject before and after a given intervention provide meaningful insights into cortical plasticity.[18] Precisely, higher MEP amplitudes represent the recruitment of a larger volume of M1 cells spared by the lesion and synchronized by TMS.[19,34] Shorter MEP latencies can indicate 2 potential intertwined changes: a better synchronicity of descending volleys, therefore a more efficient depolarization of spinal motor neurons,[34] or a better recruitment of short-latency corticocortical projections from premotor areas to the M1.[35] All these mechanisms imply that rPMS (via the induction of proprioceptive flows to the lesioned hemisphere mediated by thalamocortical and corticocortical fibers) potentially influenced the synaptic connectivity of premotor and M1 cells spared by the lesion.[4,10] This capacity of transcortical synapses to undergo long-term modifications in response to an upcoming stimulation was already reported in adults.[36] Also, basic TMS studies on rPMS action clearly reported that rPMS increased M1 excitability and influenced inhibitory mechanisms of pure cortical origin.[14,37]

The rPMS might have reactivated the descending controls acting on spinal circuitry, therefore explaining the decrease of plantar flexors resistance to stretch observed in our study. However, direct effects of rPMS at the spinal level cannot be excluded. Indeed, spasticity of plantar flexors has already been related to a possible alteration of spinal mechanisms (eg, homosynaptic depression, presynaptic inhibition acting on the Ia fiber terminals, reciprocal inhibition from the TA Ia fibers).[1,38] Therefore, a potential action of rPMS on these mechanisms could have contributed to the decrease of the plantar flexors' resistance to stretch. Such mechanisms were not tested in our study. Data in the literature remain inconclusive, with some studies suggesting an rPMS effect on presynaptic inhibition (depression of the soleus H-reflex[9]), whereas other more recent experimental-designed protocols having failed to detect any spinal effect.[10,39] Therefore, future works on the topic should precisely address how rPMS influences the mechanisms of spasticity at both the cortical and spinal levels.

Other forms of noninvasive peripheral stimulation that trigger repetitive muscle contractions and joint movements were used in the research field of physiopathology to influence neuronal

plasticity and improve motor function.[40] In children with CP, both neuromuscular electrical stimulation (muscle stimulation) and functional electrical stimulation (muscle stimulation during functional task) have improved locomotor patterns,[41,42] but changes in strength remained inconsistent.[30,43] In adults with chronic stroke, peripheral nerve stimulation (PNS) (also referred to as somatosensory stimulation) and paired associative stimulation (pairing of PNS and brain stimulation) respectively reduced intracortical motor inhibition and increased MEP amplitudes. This suggested that modulation of inhibitory pathways involving gamma-aminobutyric acid synaptic transmission within M1 and long-term potentiation-like mechanisms could be sensitive to peripheral stimulation and the origin of improvements of muscle strength and enhanced training of functional tasks.[44-49] The rPMS in our case study in CP also led to an increase of MEP amplitude (ie, an upregulation of corticospinal excitability), in line with earlier results in adults.[14,37] However, rPMS is painless compared with neuromuscular electrical stimulation, functional electrical stimulation, paired associative stimulation, and PNS because the magnetic stimuli are capable of producing muscle contractions with negligible recruitment of cutaneous and nociceptive receptors.[4,5,50-52] The massive sensory afferents that reach the frontoparietal networks involved in motor programming are not contaminated by cutaneous information and are purely proprioceptive, they are thus most relevant for motor control.[5,10] This may explain the parallel changes of clinical and TMS outcomes in our study that reflected a more efficient ankle and locomotor function.

Improvement of all gait parameters 15 days after the end of the rPMS protocol may have resulted from the transfer of ankle function improvements.[53] For example, the activation of dorsiflexors with null gain of plantar flexors' stretch reflex is necessary to perform efficient active dorsiflexion of the ankle and is crucial during the swing phase of gait to avoid foot drop and protect ankle joint integrity.[54] Plantar flexors are often overactive during gait in children with CP,[55] and the reduction of this overreactivity to stretch after rPMS might have eased the swing phase of gait. Alternatively, rPMS could have directly influenced cortical and subcortical loops involved in the neural control of walking[56] (eg, frontoparietal networks[57]). Precisely, it is known from positron emission tomography imaging that rPMS can influence such sensorimotor connectivity.[5] Plasticity in these sensorimotor networks therefore represents a possible substrate underlying gait improvement.

Study limitations

Our protocol did not include a motor-driven system to measure the resistance of plantar flexors to stretch; however, the standardized method that was used by the research therapist ensured intertrial reproducibility with a stable velocity. Also, our case study focused on the effects of rPMS at the cortical level only in the hemisphere with the lesion. Future studies should investigate both hemispheres with TMS and test the spinal circuits to provide additional insights on the mechanisms underlying motor improvements after rPMS administration.

Conclusions

Our single-subject study in CP generated interesting hypotheses on cortical and corticospinal plasticity to explain the functional improvements detected after a painless noninvasive peripheral intervention known to impact the exacerbation of the stretch reflex in spastic individuals.[1,58] Persistence of active dorsiflexion and gait changes 15 days after the end of the intervention with a return to preintervention values at 45 days supports the fact that improvements were mediated by rPMS and not by variability of measures. Our findings encourage the collection of group data in randomized controlled trials testing rPMS as an adjuvant to rehabilitation to decrease spasticity and promote motor function in CP.

Suppliers

a. Lafayette Instrument Co, 3700 Sagamore Pkwy N, Lafayette, IN 47904.
b. Magstim Co Ltd, Spring Gardens, Whitland, Carmarthenshire SA34 0HR, UK.
c. Delsys Inc, 23 Strathmore Rd, Natick, MA 01760.
d. ADInstruments Inc, 2205 Executive Circle, Colorado Springs, CO 80906.

Keywords

Cerebral palsy; Gait; Muscle spasticity; Neuronal plasticity; Peripheral nerves; Rehabilitation; Transcranial magnetic stimulation

Corresponding author

Véronique H. Flamand, OT, MSc, Centre de recherche du CHU de Québec, Axe Neurosciences, 2705 boul. Laurier, RC-9800, Québec, QC, Canada, G1V 4G2. *E-mail address:* veronique.flamand.1@ulaval.ca.

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