Neuroscience Letters 639 (2017) 192–198

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Effects of spinal cord stimulation on motor functions in children with cerebral palsy

I.A. Solopova[a,f,*], I.A. Sukhotina[b], D.S. Zhvansky[a], G.A. Ikoeva[c], S.V. Vissarionov[c], A.G. Baindurashvili[c], V.R. Edgerton[d], Y.P. Gerasimenko[d,e], T.R. Moshonkina[e,f]

[a] Institute for Information Transmission Problems, Russian Academy of Science, Moscow 127994, Russia
[b] First Pavlov State Medical University, St. Petersburg 197022, Russia
[c] Turner Pediatric Orthopedic Research Institute, Ministry of Public Health, Pushkin, St. Petersburg 196603, Russia
[d] Department of Integrative Biology and Physiology, UCLA 612, Los Angeles, CA 90095-7246, USA
[e] Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg 199034, Russia
[f] LLC Cosyma, Moscow 129164, Russia

HIGHLIGHTS

- Controlled randomized study performed in children with severe cerebral palsy.
- Transcutaneous electrical spinal cord stimulation improves motor skills.
- The stimulation increases joint range of motion.
- The stimulation decrease pathological muscle co-activation.

ARTICLE INFO

Article history:
Received 4 August 2016
Received in revised form
21 December 2016
Accepted 3 January 2017
Available online 4 January 2017

Keywords:
Cerebral palsy
Transcutaneous spinal cord electrical stimulation
Rehabilitation

ABSTRACT

Is it possible to regulate the functional properties of abnormally developed spinal neuronal locomotor networks using transcutaneous spinal cord stimulation? This question has been studied in twenty-eight participants (~9 yrs) with spastic cerebral palsy, and mainly Gross Motor Function Classification System for Cerebral Palsy level III. The participants were randomly assigned to two groups. The experimental group received transcutaneous spinal cord stimulation at two spinal levels (over T11 and L1 spinous processes), combined with locomotor treadmill training, whereas the participants of the control group received locomotor treadmill training only. After spinal cord stimulation in the experimental group we found an incremental increase in knee torque whereas in the control group this effect was absent. The amplitude of hip motion increased in both groups. A decrease of co-activation of hip and muscles of the lower extremities was observed in the experimental group while in the control group co-activation decreased only in hip muscles. The results support the idea that locomotor function can be improved significantly with the combination of training and transcutaneous spinal cord stimulation than with training alone.

1. Introduction

It is known that electrical stimulation applied to spinal cord at L2 spinal segment can induce stepping patterns in leg muscles in spinal cord injured (SCI) patients [1]. We have shown that locomotor training combined with epidural electrical spinal cord stimulation (SCS) facilitated the recovery of voluntary leg movements in motor complete SCI patients [2,3]. Recently we developed a method of electrical activating the spinal circuitry via electrodes placed on the skin overlying the lower thoracic vertebrae and demonstrated that in non-injured subjects, involuntary and voluntary locomotor-like movements can be induced and facilitated, respectively, by noninvasive transcutaneous SCS (tSCS) [4,5]. Similar positive effects of tSCS was observed in SCI patients. It was demonstrated that this neuromodulatory strategy enabled voluntary locomotor-like movements after motor complete paralysis for >1 yr [5]. Here, we hypothesized that tSCS combined with

* Corresponding author at: Laboratory of Neurobiology of Motor Control, Institute for Information Transmission Problems, Russian Academy of Science, Bolshoy Karetny 19, Moscow 127994, Russia.
E-mail address: solopova@iitp.ru (I.A. Solopova).

http://dx.doi.org/10.1016/j.neulet.2017.01.003
0304-3940/

Table 1
Subject characteristics for each treatment group.

Experimental group						Control group					
Child/gender	GMFCS	age	Ashw	GMFM-88		Child/gender	GMFCS	age	Ashw	GMFM-88	
				pre	post					pre	post
Ex1/m	II	7	1	245	245	C1/f	II	10	1	210	212
Ex2/m	II	9	2	230	245	C2/f	II	7	1	137	139
Ex3/f	II	6	1	201	205	C3/m	III	10	3	234	238
Ex4/f	III	7	1+	210	220	C4/f	III	9	1	191	194
Ex5/m	III	8	1	198	210	C5/f	III	13	2	169	174
Ex6/f	III	9	1+	190	191	C6/m	III	9	1	157	157
Ex7/f	III	10	2	162	164	C7/m	III	12	2	153	153
Ex8/m	III	8	2	146	148	C8/m	III	7	1+	141	141
Ex9/f	III	11	1	145	148	C9/f	III	10	1	122	122
Ex10/f	III	10	1+	144	190	C10/m	III	10	1	110	110
Ex11/f	III	11	2	109	112	C11/f	III	8	2	106	106
Ex12/m	IV	10	2	43	47	C12/m	III	10	3	83	83
Ex13/m	IV	11	3	34	37	C13/m	III	10	2	42	42
						C14/m	III	11	1	146	146
						C15/m	IV	11	2	90	92
mean	2.9	9.0	1.7	158.2	166.3*		2.9	9.8	1.6	139.4	140.6*
SD	0.6	1.7	0.7	65.5	67.3		0.5	1.7	0.7	50.3	51.3

GMFCS – Gross Motor Function Classification System for Cerebral Palsy; *GMFM-88* – Gross Motor Function Measure; *II = walks with limitations; III = walks using a hand-held mobility device; IV = self-mobility with limitations* [13]; *Ashw – Ashworth score for spasticity.*

* Significant differences between pre and post values within a group, ($p < 0.05$).

locomotor training can recalibrate abnormally developed neuronal networks in children to improve locomotor function.

Cerebral palsy (CP) is characterized by muscle weakness, impaired coordination of muscles and spasticity of extremities [6–8]. It was suggested, that maturation of the spinal locomotor output is impaired in children with CP [9]. Postmortem examination of children with CP show abnormalities in motor centers of the brain, including the cranial nerve motor nuclei as well as in the rostral segments of the spinal cord [10]. Magnetic resonance imaging of the spinal cord in the CP subjects with spastic diplegia have significantly less white matter area than non-injured individuals at C6/C7 and T10/T11 segments. In the same segments grey matter area of CP is normal [11]. In a rat CP model motoneuron size and the quantity of synaptic contacts are reported to be normal [12] as are the number of lumbar motoneurons and interneurons. It has also been reported that the greater the imbalance of inhibitory-excitatory connections of motoneurons the more severe the motor disorders [13]. It remains unclear, however, how much of the dysfunction can be attributed to spinal neuronal networks vs. supraspinal dysfunction.

Herein we introduced tSCS in children with CP to examine whether the neuromodulation of spinal networks could facilitate recovery of locomotor functions, i.e., functionally transform abnormal toward more functionally normal state. We compared the effects of training alone vs. tSCS combined with locomotor training on the locomotor function of individuals with CP.

2. Methods

2.1. Subjects

The Academic Council of the Turner Scientific and Research Institute for Children's Orthopedics approved this study in accordance with the Declaration of Helsinki. Parents of all participants provided informed consent in writing. Twenty eight children with CP (spastic diplegia) (9.4 ± 1.7 yrs., mean ± SD) participated in the study. Most of the CP subjects were rated as level III according to classification of GMFCS [14] (Table 1). Ten non-injured normally developed children of the same age (8.7 ± 2.1 yrs., 6 male, 4 female) also were tested. All CP participants previously (no later than 2–5 yrs. before the study) had surgical interventions (neurosurgical and/or orthopedic) to decrease the spasticity and contractures. During the study, none of the participants was treated with anti-spastic medication. No botulinum toxin injections within the 6 months before the study. The degree of mental development was evaluated by Raven's test [15]. A mean score of >70% was required to participate in the study (corresponding to middle or higher level of mental development). All participants were sociable and able to accurately perform the required tasks. Exclusion criteria were severe contracture of the lower limbs, which impeded rehabilitation and required surgical orthopedic treatment, fractures, osteoporosis, thromboembolic disease, instability of the cardiovascular system, degradation of intellectual development.

Children were randomly assigned to one of two groups (Table 1). The randomization was performed by technical personnel who were uninformed about the details of the study. The Experimental group (n = 13) received 15 sessions of training combined with tSCS over a period of 3 weeks. During each training session, the child was placed in Lokomat device (Hocoma, Switzeland). Game-like augmented performance feedback exercises were used to increase motivation and effort of participants of both groups during treatment and tests. The protocol of tSCS was based on preclinical studies [16]. Initially the tSCS was delivered at L1 level for 5 min in upright posture. The participants were instructed to keep a normal upright posture. The level of body weight support was selected individually so that the child could stand while maintaining equilibrium. During the first 10 min of locomotor training tSCS was applied at T11 vertebral level, followed by the combination of T11 and L1 stimulation for the next 10 min. Afterward the stepping performance was continued for 20 min without stimulation. Locomotor training was performed at a treadmill speed of ~1 km/h. The children of the Control group (n = 15) (Table 1) received only locomotor training with Lokomat (40 min) without tSCS for 15 sessions.

2.2. Stimulation

Transcutaneous SCS was delivered using a 2.5-cm round electrodes (Syrtenty®, China) placed midline at the T11, and L1 spinous processes as cathodes (Fig. 1A, B) and two $5.0 \times 8\,cm^2$ rectangular plates (Syrtenty®) placed symmetrically on the skin over the iliac crests as anodes. Biphasic rectangular 1.0 ms pulses (30 Hz), modulated frequency of 10 kHz were used. The main intensity of

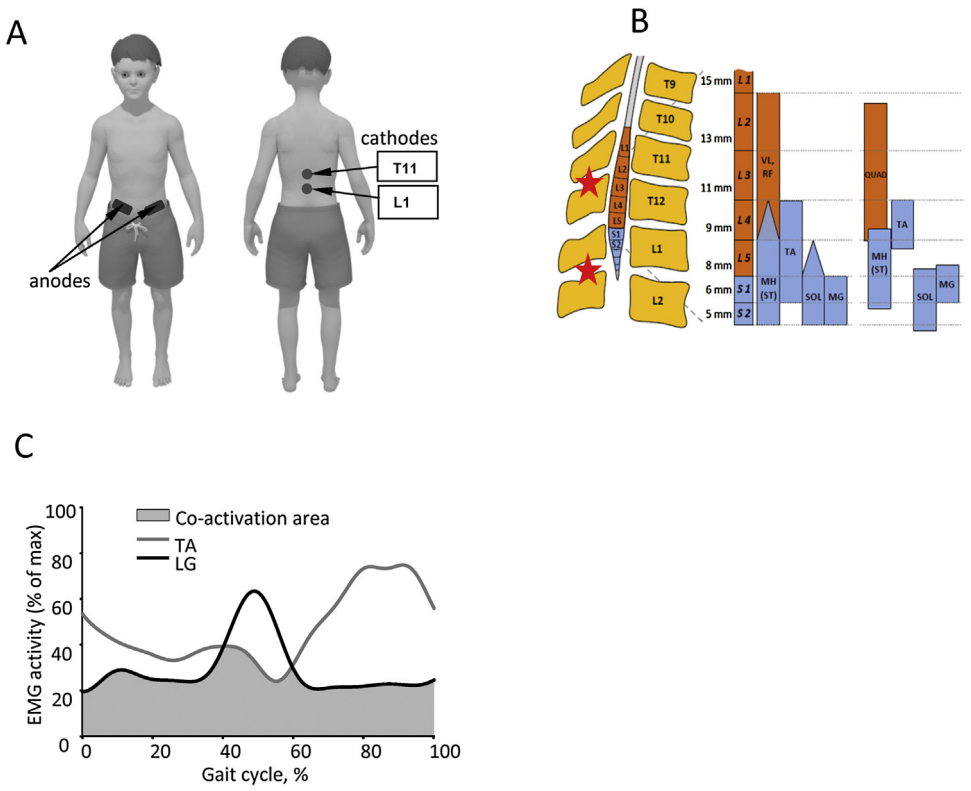

Fig. 1. Technology of tSCS and the method of muscle co-activation (CA) computation. A. Anodes and cathodes position on the child. B. Scheme of cathodes position (asterisks) relatively to spinal segments and location of the motor pools based on the segmental charts, modified from [22]. C. Illustration of CA index computation for two antagonist leg muscles (TA/LG).

stimulation ranged from 10 to 50 mA for most children. Intensity was chosen individually, ranging from 5 to 10% below threshold of muscle contraction, and was well tolerated by all the participants.

2.3. Outcome measurements

All CP children were tested before and after treatment. The leg spasticity was examined using a modified Ashworth scale [17]. Evaluation of the level of motor functions was provided based on GMFM-88 (Gross Motor Function Measure) scale [18].

Calculation of isometric force in flexors and extensors of hip as well as of knee muscles performed using the L-FORCE test of Lokomat software. This assessment was made at 30° hip flexion and 45° knee flexion. A participant was instructed to generate a maximal isometric effort in flexor or extensor muscles of the corresponding joint.

Evaluation of active range of the movements for flexion/extension in hip and knee joints was performed using the L-ROM test, as directed by Lokomat software. The child was in a suspended position when instructed to move the hip and knee joints volitionally through the maximal range.

Electrical leg muscle activity (EMG) (rectus femoris (RF), biceps femoris (BF), lateral gastrocnemius (LG) and tibialis anterior (TA)) was recorded with a telemetric system (MEGA, Finland). EMG activity was tested during air stepping with 100% body weight support by Lokomat device as well as during unaided stepping on Lokomat at the subjects' maximal speed without body weight support, but supported from a horizontal rail, as needed. These two types of walking were chosen because they differ in terms of the tasks to be solved by the nervous system. During air stepping there were no propulsion task nor weight support task, and in such cases thigh muscles are typically more active. During treadmill stepping ankle muscles were more involved into activity because the support afferentation was presence.

For assessment of EMG amplitudes, raw EMG signals were numerically rectified, low-pass-filtered with a zero-lag Butterworth filter at 20 Hz cutoff. Co-activation (CA) index of two agonist–antagonist muscle couples (RF/BF, TA/LG) for both legs were calculated following the method described by *Unnithan* et al. [19]. Raw EMG data were normalized to the largest value of activation observed in each muscle across all trials for each subject. In the most cases the largest muscle activity occurred in the L-FORCE trial, but sometimes during treadmill walking. EMG data were based on 10 consecutive step cycles. Integration of the overlapping area between the two normalized linear envelopes defined the CA index (Fig. 1C).

2.4. Statistical analysis

Descriptive statistics included means and standard error (SE). The statistical analysis was performed by Statistica 10 software. The non-parametric Mann-Whitney *U* test was used to compare clinical scores and biomechanical values (EMG, L-FORCE, L-ROM,) before and after treatment. The Wilcoxon test was performed to compare the same parameters before and after treatment within each group. A level of $p < 0.05$ was accepted as statistically significant.

3. Results

3.1. Clinical score and Lokomat tests

There were no significant group differences in the baseline clinical measurements (GMFCS level, Ashworth score) (Table 1). After treatment, there were significant increases in the GMFM-88 score in the tSCS group ($p < 0.002$) and in the control group ($p < 0.03$), but

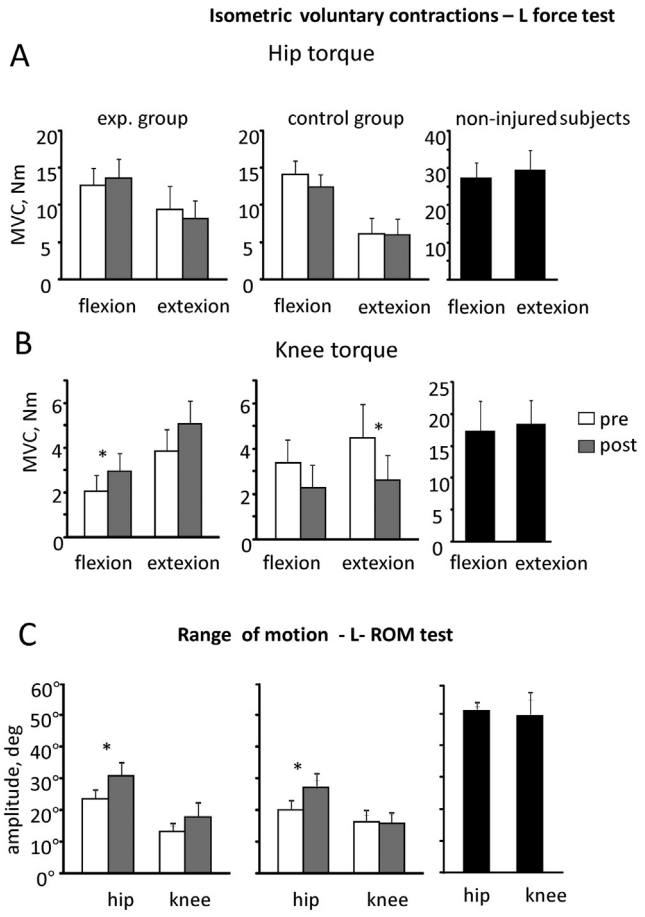

Fig. 2. Results of Lokomat tests. A. Amplitude of maximal voluntary contraction (MVC) of hip flexors and extensors (mean ± SE). B. Amplitude of MVC of knee flexors and extensors. C. Range of motion in hip and knee before and after treatment in the experimental and the control groups, and in non-injured children. Asterisks denote significant differences in the motor functions before and after treatment.

this increase was significantly higher in the tSCS group (post-pre $p < 0.01$). The increase of standing and walking scores (GMFM-88 dimensions D and E, respectively) was insignificantly higher in the tSCS group than in group only receiving locomotor training (Fig. S1, Table S1). The change in total GMFM-88 score was significantly correlated with increase of walking, but not the standing score (Fig. S1). Transcutaneous SCS induced meaningful clinical differences in total, Dimension D and Dimension E GMFM score while without stimulation, differences were less than the critical values (Table S1). After treatment, there were no changes of spasticity in any participant either group, as measured by the Ashworth score (Table 1).

Because these participants were diplegic the results for right and left legs were averaged. No differences between groups were found in the knee or hip torque tests (L-FORCE) before treatment. Maximal hip and knee flexion and extension torques of both groups were significantly lesser than of non-injured subjects (Fig. 2A,B). Neither maximal hip flexion or extension torque changed in the control or the experimental groups after treatment. Maximal knee flexion, but not extension, torque increased after tSCS in the experimental group only ($p < 0.01$, Fig. 2B). Maximal knee extension torque was unchanged in the experimental group and decreased in the control group ($p < 0.05$, see individual changes for knee flexion and extension in Fig. S2).

Range of hip movements increased in both groups whereas knee range was unchanged in both groups. The range of hip or knee motion for the participants of both groups was significantly less than in non-injured subjects both before ($p < 0.001$) and after treatment ($p < 0.001$) (Fig. 2C).

3.2. Muscle co-activation during stepping movements

The mean treadmill stepping speed before treatment was similar in the experimental and the control groups: 1.45 ± 0.12 km/h and 1.49 ± 0.10 km/h, respectively ($p = 0.85$). Non-injured children performed such walking with a significantly higher speed- 2.7 ± 0.1 km/h ($p < 0.001$). After treatment, 5 children from the experimental group and 5 children from the control group had higher walking speeds, but on average no significant speed changes were observed in either group. The mean period of air-stepping movements in CP children before treatment was 2.7 ± 0.2 s and 2.9 ± 0.2 s in the experimental and the control groups, respectively which was significantly longer than in non-injured subjects – 2.1 ± 0.1 s ($p < 0.01$). After treatment the cycle period during air stepping became slightly shorter in each group (2.5 ± 0.2 sec and 2.7 ± 0.3 sec for the experimental and the control group, respectively), but these decreases were not significant ($p = 0.24$ for the experimental and $p = 0.39$ for the control group).

Abnormal levels of muscle CA, i.e., showing simultaneous activation of agonist and antagonist muscles, were observed in the experimental and the control group (Figs. 1C and 3A). In CP children, we typically observed higher CA index values compared to non-injured subjects during both air-stepping and treadmill walking (Fig. 3B and C). The co-activation for proximal and distal agonist-antagonist muscles was significantly higher during stepping on the treadmill than during air stepping for non-injured children ($p < 0.05$ for RF/Bf and $p < 0.01$ for TA/LG), as well as for CP children ($p < 0.01$ for RF/Bf and $p < 0.003$ for TA/LG) (Fig. 3B, C). At the beginning of treatment, there were no differences in CA of either proximal or distal muscles between the experimental and the control groups for either mode of stepping. After treatment, the decrease of CA index in proximal and distal muscles occurred in the experimental group for both types of stepping motion, whereas in the control group CA index decreased in proximal muscles only (Fig. 3B and C).

4. Discussion

Previous studies of representative groups of children with CP, with mainly a level III deficit have shown maximal improvement of motor functions up to the age of 10 years with standard rehabilitation including mechanotherapy; afterwards motor skills did not increase and in some cases even decreased [20]. Using the GMFM-88 scale we have shown that improvements occurred in less than 50% of the cases in the control group, while in the experimental group 92% of the subjects showed improved motor skills. These changes were “clinically meaningful” only for the experimental group (Table S1).

Degradation of motor activity in children with CP is linked to with pathology of supraspinal as well as of spinal networks connections during ontogenesis [10,11]. One of the functional consequences of the abnormal CP development is the level of abnormal reciprocal inhibition of Ia afferents, presynaptic inhibition and non-reciprocal Ib inhibition a phenomenon largely attributable to spinal networks [21]. We have demonstrated that after tSCS and step training the amplitude of movement in both the hip and knee joints increased (Fig. 2B). This observation is consistent with the reduction of co-activation of proximal and distal leg muscles (Fig. 3). This suggests that tSCS, combined with neuro-mechanotherapy, had positive influences on coordination not only for proximal, but for distal muscles as well. Previous studies have shown that improved locomotor performance is closely associated with improved coordination of motor pools [13]. Transcutaneous SCS at T11 and L1

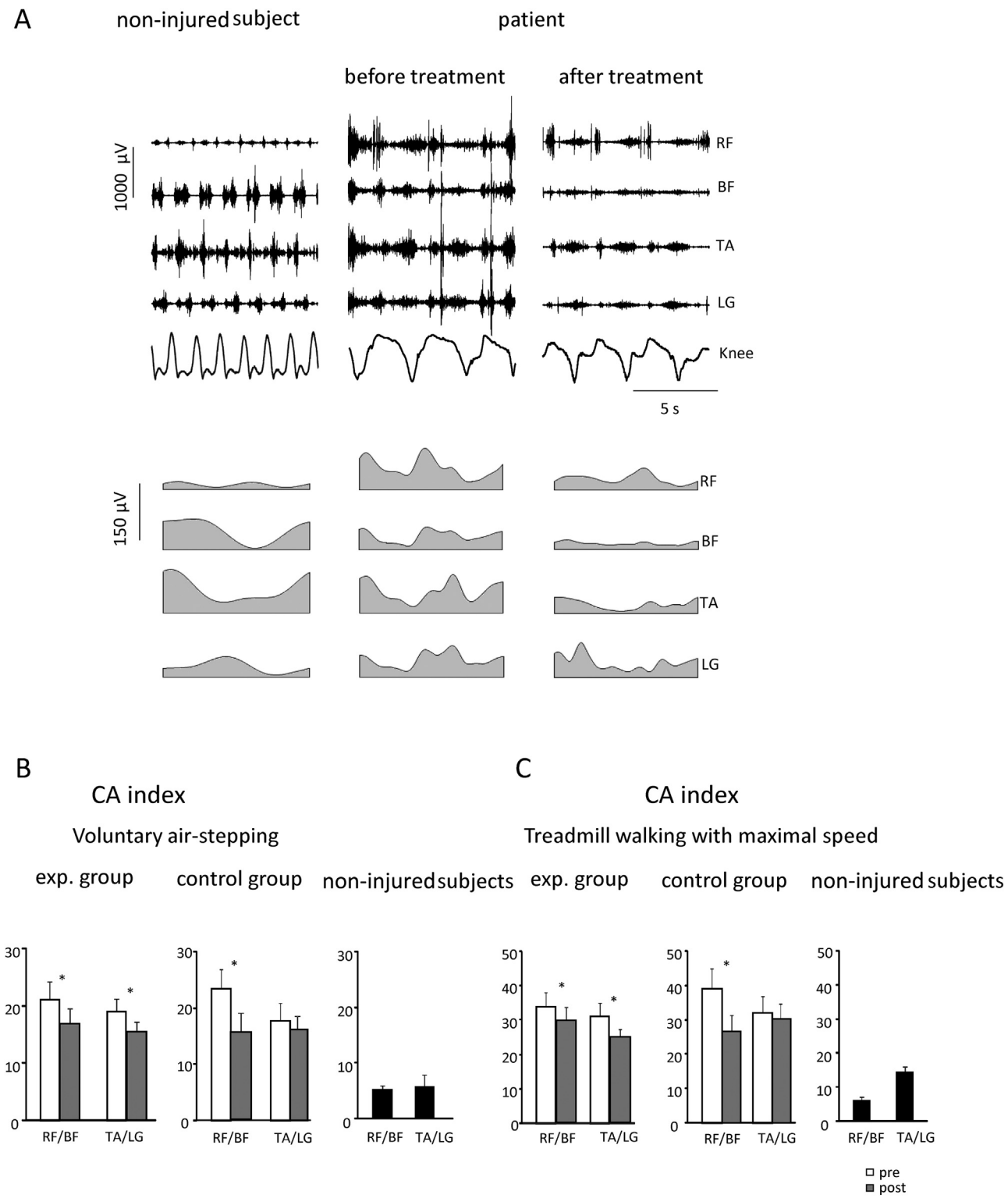

Fig. 3. Muscle CA during stepping before and after treatment. A. Examples of motor patterns during treadmill walking with maximal speed and ensemble averaged (across 10 movement cycles) EMG envelopes of leg muscles (on the bottom) in one representative non-injured subject and in one of the best children with CP of the experimental group before and after treatment. EMG and knee joint angle of right leg are represented. B. CA values (mean ± SE) for hip (RF/BF) and ankle (TA/LG) muscle at voluntary air-stepping in non-injured persons and in participants of both groups before and after treatment. C. The same for treadmill walking with maximal speed. Asterisks denote significant differences before and after treatment.

vertebral levels of proximal and distal motor pools in paralyzed subjects are facilitated (Fig. 1B) [22]. This effect is evident in spinal motor evoked potentials of proximal and distal leg muscles to single stimulation pulses [23]. We also have found that epidural SCS combined with training can increase hand grip force in spinal patients with cervical injuries [24]. This suggest that similar interventions of training and cervical tSCS could also benefit for children with CP.

Epidural SCS at T10-T12 spinal segment in CP children with spastic lower paraparesis, stimulated from half year, up to 9 years, has been reported to have reduced postural tonic reflexes and less mus-

cle tone as determined by Ashworth scale [25,26]. We did not find a significant decrease in spasticity after tSCS.

At present, we have no data on the question of whether the improvement observed in response to spinal cord neuromodulation can be attributed to spinal or supraspinal networks, but most likely, it represents a combination of both. The observation that paralyzed animals can regain full weight-bearing stepping after step training is consistent with the spinal networks playing a significant role in the improved motor function in the present study [27]. The restoration of stepping after spinal cord transection with epidural SCS has been reported to correlate with appearance of greater polysynaptic reflexes induced by S1 spinal segment stimulation [28]. In patients with spinal cord injury it was demonstrated that SCS resulted in improved polysynaptic responses in leg muscles to single spinal stimulus, suggesting some reorganization of neuronal network [29].

The present findings on the effects of SCS combined with locomotor training on motor function in children with CP are suggestive, but not conclusive due to (1) the treatments and testing were not blinded (2) GMFM-88 scale is a subjective test, and (3) there were no repeated baseline measures. These findings, however, provide encouraging data that tSCS is a novel intervention that could improve motor functions and significantly improve the quality of lives of children when combined with well-developed rehabilitative strategies. Therefore, further studies should receive a high priority.

5. Conclusions

Our findings of a stable improvement of motor functions in children with CP in response to tSCS when combined with training suggest that some functional improvement of the spinal and supraspinal networks that control locomotor functions were induced. These findings need to be explored further with more quantitative tools to assess more comprehensively the more responsive neuro-mechanical properties observed here. Further studies are also indicated given the observations that the level of spinal neural plasticity in response to a neonatally induced spinal abnormality seems to be significantly greater than when a sudden traumatic injury occurs in an adult [30]. Studies using animal models of cerebral palsy [12] could facilitate a more basic mechanistic understanding of the neurobiological underpinnings of neonatal and adult neuroplasticity of cerebral palsy.

Conflict of interest statement

VRE and YG – researchers on the study team hold shareholder interest in NeuroRecovery Technologies and hold certain inventorship rights on intellectual property licensed by The Regents of the University of California to NeuroRecovery Technologies and its subsidiaries.

Acknowledgements

This work was supported by the Grant of the Ministry Education and Science of the Russian Federation (N 14.576.21.0020, agreement RFMEFI57614X0020). The authors are grateful to Tatiana Bulgakova for diligent work with children during training and tests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2017.01.003.

References

[1] M. Dimitrijevic, Y. Gerasimenko, M. Pinter, Evidence for a spinal central pattern generator in humans, Ann. N. Y. Acad. Sci. 860 (1998) 360–376.
[2] S. Harkema, Y. Gerasimenko, J. Hodes, J. Burdick, C. Angeli, et al., Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study, Lancet 377 (2011) 1938–1947.
[3] C.A. Angeli, V.R. Edgerton, Y.P. Gerasimenko, S.J. Harkema, Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans, Brain 137 (5) (2014) 1394–1409.
[4] R.M. Gorodnichev, E.A. Pivovarova, A. Puhov, S.A. Moiseev, A.A. Savokhin, et al., Transcutaneous electrical stimulation of the spinal cord: a noninvasive tool for the activation of stepping pattern generators in humans, Hum. Physiol. 38 (2) (2012) 158–167.
[5] Y.P. Gerasimenko, D.C. Lu, M. Modaber, S. Zdunowski, P. Gad, et al., Noninvasive reactivation of motor descending control after paralysis, J. Neurotrauma 32 (24) (2015) 1968–1980.
[6] D.L. Damiano, T.L. Martellotta, J.M. Quinlivan, M.F. Abel, Deficits in eccentric versus concentric torque in children with spastic cerebral palsy, Med. Sci. Sports Exerc. 33 (1) (2001) 117–122.
[7] J.R. Engsberg, S.A. Ross, K.S. Olree, T.S. Park, Ankle spasticity and strength in children with spastic diplegic cerebral palsy, Dev. Med. Child Neurol. 42 (1) (2000) 42–47.
[8] S.K. Stackhouse, S.A. Binder-Macleod, S.C. Lee, Voluntary muscle activation, contractile properties, and fatigability in children with and without cerebral palsy, Muscle Nerve 31 (5) (2005) 594–601.
[9] G. Cappellini, Y.P. Ivanenko, G. Martino, M.J. MacLellan, A. Sacco, et al., Immature spinal locomotor output in children with cerebral palsy, Front. Physiol. 478 (7) (2016) 1–21.
[10] V.D. Levchenkova, K.A. Semenova, Contemporary views of the morphological basis of infant cerebral palsy, Zhurnal nevrologii i psikhiatrii imeni SS Korsakova 112 (7) (2012) 4–8 (In Russian).
[11] J.J. Noble, Musculoskeletal and Spinal Cord Imaging in Bilateral Spastic Cerebral Palsy, Diss., King's College, London, 2014.
[12] M.R. Marques, F. Stigger, E. Segabinazi, et al., Beneficial effects of early environmental enrichment on motor development and spinal cord plasticity in a rat model of cerebral palsy, Behav. Brain Res. 263 (2014) 149–157.
[13] E.G. Condliffe, D.T. Jeffery, D.J. Emery, M.A. Gorassini, Spinal inhibition and motor function in adults with spastic cerebral palsy, J. Physiol. 594 (10) (2016) 2691–2705.
[14] R. Palisano, P. Rosenbaun, S. Walter, S. Russel, E. Wood, B. Galuppi, Development and reliability of a system to classify gross motor function in children with cerebral palsy, Dev. Med. Child Neurol. 39 (4) (1997) 214–223.
[15] J.C. Raven, J.H. Court, J. Raven, Manual for Raven's Progressive Matrices and Vocabulary Scales: Section 2: Coloured Progressive Matrices: Edition, Oxford Psychologists Press, Oxford, 1995.
[16] G. Courtine, Y. Gerasimenko, R. van den Brand, et al., Transformation of nonfunctional spinal circuits into functional states after the loss of brain input, Nat. Neurosci. 12 (10) (2009) 1333–1342.
[17] R.W. Bohannon, M.B. Smith, Interrater reliability of a modified Ashworth scale of muscle spasticity, Phys. Ther. 67 (2) (1987) 206–207.
[18] D.J. Russell, P.L. Rosenbaum, D.T. Cadman, C. Gowland, S. Hardy, S. Jarvis, The gross motor function measure: a means to evaluate the effects of physical therapy, Dev. Med. Child Neurol. 31 (3) (1989) 341–352.
[19] V.B. Unnithan, J.J. Dowling, G. Frost, B. Volpe Ayub, O. Bar-Or, Cocontraction and phasic activity during gait in children with cerebral palsy, Electromyogr. Clin. Neurophysiol. 36 (1996) 487–494.
[20] S.E. Hanna, D.J. Bartlett, L.M. Rivard, D.J. Russell, Reference curves for the Gross Motor Function Measure: percentiles for clinical description and tracking over time among children with cerebral palsy, Phys. Ther. 88 (5) (2008) 596–607.
[21] F.M. Filloux, Neuropathophysiology of movement disorders in cerebral palsy, J. Child Neurol. 11 (suppl. (1)) (1996) S5–S12.
[22] D.G. Sayenko, D.A. Atkinson, T.C. Floyd, R.M. Gorodnichev, T.R. Moshonkina, et al., Effects of paired transcutaneous electrical stimulation delivered at single and dual sites over lumbosacral spinal cord, Neurosci. Lett. 609 (2015) 229–234.
[23] D.G. Sayenko, D.A. Atkinson, C.J. Dy, K.M. Gurley, V.L. Smith, et al., Spinal segment-specific transcutaneous stimulation differentially shapes activation pattern among motor pools in humans, J. Appl. Physiol. 118 (11) (2015) 1364–1374.
[24] D.C. Lu, V.R. Edgerton, M. Modaber, N. AuYong, et al., Engaging cervical spinal cord networks to reenable volitional control of hand function in tetraplegic patients, Neurorehabil. Neural Repair 30 (10) (2016) 951–962.
[25] A.V. Dekopov, V.A. Shabalov, A.A. Tomsky, M.V. Hit, E.M. Salova, Chronic spinal cord stimulation in the treatment of cerebral and spinal spasticity, Stereotact. Funct. Neurosurg. 93 (2) (2015) 133–139.
[26] V.A. Shabalov, A.G. Bril', A.L. Kurenkov, A.V. Bystrov, The use of chronic epidural electrostimulation of the spinal cord in children with spastic diplegia– a type of infantile cerebral palsy, Zh. Vopr. Neirokhir. Im. N. N. Burdenko 3 (2000) 2–6 (In Russian).
[27] R.D. De Leon, J.A. Hodgson, R.R. Roy, V.R. Edgerton, Full weight-bearing hindlimb standing following stand training in the adult spinal cat, J. Neurophysiol. 80 (1) (1998) 83–91.

[28] I. Lavrov, Y.P. Gerasimenko, R.M. Ichiyama, G. Courtine, H. Zhong, et al., Plasticity of spinal cord reflexes after a complete transection in adult rats: relationship to stepping ability, J. Neurophysiol. 96 (4) (2006) 1699–1710.
[29] T.R. Moshonkina, I.N. Bogacheva, N.A. Scherbakova, A.A. Savohin, Yu.P. Gerasimenko, A.N. Makarovski, Effects of spinal cord electrical stimulation in patients with vertebrospinal pathology, Bull. Exp. Biol. Med. 153 (1) (2012) 16–20.
[30] N.J. Tillakaratne, J.J. Guu, R.D. de Leon, A.J. Bigbee, N.J. London, et al., Functional recovery of stepping in rats after a complete neonatal spinal cord transection is not due to regrowth across the lesion site, Neuroscience 166 (1) (2010) 23–33.