Andreas Hahn*, Susan Moeller, Arne Schlausch, Matilda Ekmann, Gautier de Chelle, Marie Westerlund, Frank Braatz and Winfried Mayr

Effects of a full-body electrostimulation garment application in a cohort of subjects with cerebral palsy, multiple sclerosis, and stroke on upper motor neuron syndrome symptoms

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Abstract

Objectives: Dysfunction of the central nervous system may inflict spastic movement disorder (SMD). Electrical stimuli were identified as promising therapeutic option. Electrical stimulation provided by a 58-electrode full body garment was investigated based on data from regular trial fittings.
Methods: Data from 72 testees were investigated. Age averages 36.6 (19.8) ys with 44 females. The cohort spans infantile cerebral paresis (CP) (n=29), multiple sclerosis (MS) (n=23) and stroke (n=20). Data were stratified by etiology and an entry BBS Score<45.
Results: Effect sizes (Cohen`s d) related BBS, TUG, FGA, 10mWT, WMFT, EQ5D5L and Pain. Significance levels are indicated by *: p<0.05, **: p<0.01, ***: p<0.001, (t): p<0.1: CP: 1.64***, 0.29*, 1.59***, 0.76(t), 1.00***, 0.5*, 1.28***; MS: 1.83***, 0.83***, 1.28**, 1.07***, 0.93*, 1,11**, 0.78*; Stroke: 1.28**, 0.78**, 0.89, 0.92**, 0.71, 1.26*, 0.78*.
Conclusions: Multi-site transcutaneous electrical stimulation may increase ambulation related skills in subjects with SMD stemming from CP, MS and stroke. The results indicate effects on static and dynamic balance, fall risk, mobility, upper extremity improvement and an overall increase in health utility and a reduction in spasticity related pain. Effects are immediate as well as sustained. These results may inspire individual trial fittings and inform further controlled trials.

Keywords: full-body garment; neuromodulation; spasticity; spasticity induced movement disorder

***Corresponding author: Andreas Hahn**, PhD, MSc, Ottobock Healthcare Products GmbH, Brehmstrasse 16, AT-1110 Vienna, Austria,
E-mail: Andreas.Hahn@ottobock.com. https://orcid.org/0000-0003-0918-8428
Susan Moeller, Academy, Otto Bock HealthCare Deutschland GmbH, Duderstadt, Germany
Arne Schlausch, Clinical Research & ServicesOtto Bock HealthCare Deutschland GmbH, Duderstadt, Germany
Matilda Ekmann and Marie Westerlund, Clinical Research, Exoneural Network AB, Danderyd, Sweden
Gautier de Chelle, Médecin MPR Centre de Santé ROSSETTI, Nice, France
Frank Braatz, Private Hochschule Göttingen, Göttingen, Germany
Winfried Mayr, Medical University Vienna, Vienna, Austria

Background

Upper motor neuron syndrome (UMNS)

Impairments, disease, or injuries to the central nervous system may inflict upper motor neuron syndrome [1].

By definition spasticity is characterized by a velocity-dependent increase of muscle tone acting against passive elongation. Clinically it is primarily identified as increased resistance against passive muscle lengthening. It is often associated with other phenomena like involuntary flexion or extension movements, clonus, dystonia or increased reflex responses. Such a condition may be accommodated by a broad range of symptoms often referred to as spastic syndrome [2].

The increase in the excitability of the muscle stretch reflex is attributed to abnormal activity of muscle spindles in combination with innervations of the extrafusal muscle fibers at the spinal level. Those are under influence of supraspinal inhibitory and facilitatory pathways, usually altered by the UMNS. The reflex hyperexcitability develops over a varying time period after the primary brain or spinal cord lesion and involves adaptation in spinal neuronal networks caudal to the lesion. There is evidence that in humans, the reduction of spinal inhibitory mechanisms, in particular in disynaptic reciprocal inhibition, plays a role in this respect. The increased muscle stretch reflex is assumed to be caused by an altered balance in intra- and extrafusal fiber innervation due to loss of inhibitory supraspinal control. The delayed onset of spasticity after lesion and the often-observed reduction in reflex excitability later over time

suggest plastic short- and midterm changes in the central nervous system after brain or spinal lesion. Most likely, multiple mechanisms concur in the development of human spasticity; a detailed understanding of the relevant processes remain to be further elucidated together with a multimodal assessment and intervention methods for clinical practice [2].

The motoric consequences are often referred to as spastic movement disorder (SMD) [3] observed, amongst others, in stroke, multiple sclerosis (MS), cerebral palsy (CP), spinal cord (SCI) and traumatic brain injuries (TBI). If undertreated, it may lead to significant permanent functional impairment, pain, risk of falling and severe social dysfunction [2].

Clinical management of UMNS symptoms – and here specifically the management of spasticity, spasms and related pain – includes a broad range of pharmaceutical treatments accompanied by training and physiotherapy [4].

Electrical stimulation has been used frequently as an additional treatment. Various stimulation forms (TENS, TES) have shown localized effects in reducing spasticity [5]. The mechanisms here are believed to stem from sub-motor threshold afferent stimulation contributing to the improved control of the impaired reflex control on the spinal level [5]. These treatments are often limited by the precision required to place the electrodes adequately and a related loss of patient compliance [6].

In *2012,* Lundqvist presented Elektrodress 100 (today EXOPULSE Mollii Suit), a full-body garment consisting of a jacket, pants, and control unit with 58 embedded electrodes [7]. This arrangement stimulates neurons in dermatomes and myotomes of up to 40 muscle groups. Apart from overcoming the challenges with electrode placement, it is believed that the simultaneous stimulation of different anatomical regions and their afferent nerves can lead to pronounced effects on processing in both spinal and supraspinal interneuron networks.

A main cause for manifestation of spasticity lies in alterations in suprasegmental control input to segmental interneuron processing and central state of excitability [8]. Substitution of missing supraspinal input by artificial peripheral afferent input via electrical stimulation has been identified as a promising modality. It has been addressed in various research efforts, based on invasive, predominantly epidural, or non-invasive stimulation systems [9]. In dependence of recruited afferent neuron pools and frequency of activation patterns, inhibitory and excitatory components of the segmental interneuron processing can be influenced towards reducing or elevating the central state of excitability [10]. This can have considerable influence on the relief of neuropathic pain, modification of spasticity and augmentation of impaired voluntary motor control. Though there is no one-for-all solution and there are patients that cannot accomplish any benefit at all, individual improvements, based on personalized setups and parameter sets, can range from moderate to substantial, depending on the nature of the lesion and the respective physiological conditions [11].

The distributed electrode placement in a functional garment, like the EXOPULSE Mollii Suit, provides spatial selectivity of afferent neural inputs to spinal interneuron networks and thus the option to individualize the intervention protocol. Stimulation patterns may be administered more specifically to neurons in regions where the peripheral movement disturbances occur. Inhibitory mechanisms like reciprocal inhibition [12] or post-activation depression [13] are addressed in the modification of spasticity. Reciprocal inhibition is induced by stimulation of the proprioceptive afferents of the antagonist of the spastic agonist muscle. Proprioceptive afferent neurons have a lower stimulation threshold than efferent motor neurons and thus can be activated with some selectivity. The afferent signal activates inhibitory circuits in the segmental spinal interneuron networks and blocks activation of motor neurons of the agonistic (spastic) muscle. At the same time, it can amplify residual motor control of the agonist, but not in any case with strong dependence on the manifestation of the underlying neural damage. Excitatory mechanisms and an increase in the central state of excitability are the main targets in the augmentation of movement functions. Techniques for the modification of central interneuron processing via artificial afferent input are known as neuromodulation [9, 14].

The EXOPULSE Mollii Suit was clinically investigated in a series of exploratory clinical trials. Ertzgaard et al. [15] investigated a mixed cohort of 31 CP and stroke subjects in a randomized sham-controlled cross-over trial. During intervention, improvements in a 10 m walk test were observed, and Goal Attainment Scores (GAS) improved overall. On the other hand, the trial was plagued by a high number of non-compliances and Ertzgaard and colleagues concluded that the absence of significance at group level did not rule out the possibility of relevant individual improvements, which had also been observed. Bakaniene et al. [16] investigated 16 CP children in a parallel group design, comparing the effects to classical high intensity physiotherapy. Gross motor function skills improved in both groups with no significant differences found between the groups. No meaningful changes in patient reported outcome measures (PROMs) and spasticity were found.

Hedin et al. [17] revealed significant improvements in spasticity and PROMs in an investigation of 16 CP children. The trial was plagued by 50 % drop-out. Drop-out was attributed to inconvenience in using the suit (3), no improvement (3), inability to follow instructions (1) and problems with

epilepsy (1). Palmcrantz et al. [18] reported high compliance in a cohort of 20 stroke subjects and relevant and significant improvement of wrist flexor spasticity. However, the effects were not mirrored by findings in the Ashworth Scale. Functional tests like the Berg Balance Scale, 10 m walk test and 6-min walk test were silent. Pennati et al. [19] reported no effects in the same cohort on group level immediately after a stimulation period of 60 min. Flodstroem et al. [20] report on improvements in the total score of the Canadian Occupational Performance Measure, in pain and to a smaller extent in activity and participation in a cohort of six children with cerebral palsy.

While showing some of the technology´s potential, this evidence reported so far on the whole remains incoherent and is sometimes contradictory. The studies are often plagued by severe drop-out or non-compliance. The effects are not always stratified or sub-analyzed according to etiology or other concomitant factors. Investigated groups are often very heterogeneous, with wide ranges of functional impairment levels and cognitive capabilities. Based on a series of interviews with children and parents, Bourke-Taylor et al. [21] reported that different levels of compliance with the suit may be related to children´s capability to communicate and report on possible discomfort or pain.

The evidence is accompanied by anecdotal or video-reported evidence of individual functional improvement [22].

In response to the clinical findings, several technical improvements were implemented to increase overall device acceptance and efficacy. Reliability of wired connections from the control unit improved significantly. More importantly, stimulation patterns were developed allowing for a higher degree of individual freedom in specifying the spastic target region and a much greater use of the multi-site stimulation possibilities of the suit including near fully body stimulation.

The EXOPULSE Mollii Suit is a class IIa certified electrical medical device with the following intended uses: relaxation of tense and spastic muscles; activation of muscles, increasing local blood circulation; symptomatic relief of chronic pain; the EXOPULSE Mollii Suit is intended for use in the home environment [23].

Objectives

Earlier investigations using the EXOPULSE Mollii Suit led to encouraging, however, heterogeneous results. It is the objective of this investigation to explore potential clinical benefits in walkers suffering spastic movement disorder due to upper motor neuron lesion caused by infantile cerebral palsy, multiple sclerosis, or stroke based on an improved version of the device and the applied stimulation pattern. It is a further objective of this investigation to explore direct effects on spasticity induced movement disorders. It is also the objective of this investigation to inform on sensitive outcome measures that may be utilized in subsequent controlled studies.

Methods

Data collected in regular routine trial fittings were retrieved from certified orthotic workshops and clinics. Participants are routinely asked to sign informed consent for subsequent scientific analysis. When the subject was a minor, the legal representative of the child is asked to consent. De-personalized data are collected electronically and pooled. Analysis was approved by the ethics committee of the Medical University Göttingen (17/1/23).

Subjects eligible for analysis were required to be indicated as cognitively able to follow instructions and verbally able to inform on discomfort. Subjects' etiology was restricted to stroke, multiple sclerosis, or cerebral palsy. Subjects were required to possess gross motor function classification scale (GMFCS) level 1 to 3 or being able to walk with or without walking aids. Subjects were classified as children when aged below 18 at the baseline assessment.

Outcome measures

To detect and quantify the individual clinical benefit, subjects underwent several validated assessments. The Timed Up and Go (TUG) test assesses mobility, balance, walking ability and falls risk. The instrument has been validated in elderly adults in a large set of etiologies; threshold values are associated with risk of falling. Minimal detectable difference in chronic stroke is reported to be 2.9 s, with a cut-off value of <14 s indicating an increased risk of falling [24].

The Berg Balance Scale (BBS) is a 14-item objective measure scored from 0 to 56 to assess static balance and risk of falling in adults. Threshold values allow to distinguish subjects with increased (<45) and very high (<40) risk of falling. A derivative, the Pediatric Balance Scale, reduces evaluation durations to account for reduced attention periods in a pediatric population (Minimal Detectable Change (MDC) total scale 1.59 points) [24].

The 10-m walk test (10mWT) [42] assesses walking velocity over a short distance. The minimal clinically important difference (MCID) is reported to be ranging from 0.05 m/s (small) to >0.13 m/s. The derived velocities allow to conclude on functional mobility, e.g., on the basis of community walking categorizations following the Perry classification (<0.4 m/s: non-community walker; 0.4 m/s to 0.8 m/s: limited community walker; >0.8 m/s: unlimited community walker) [25].

The Functional Gait Assessment (FGA) is a ten-item functional score that is investigator rated, assessing the performance of multiple motor tasks while walking on a four-level scale. The test is an improvement of the Dynamic Gait Index with improved reliability and a reduction of ceiling effects. MDC is reported to be 4.2 points in stroke. The score has predictive capacity with respect to risk of falling, with scores of <23 indicating increased risk of falling in community-dwelling older adults [24].

The Wolf Motor Function Test (WMFT) is an upper extremity motor ability test. In the version used in this assessment, strength-based items were omitted. MCID is reported to be indicated when change increases by 17 % on the dominant side and by 20 % on the non-dominant side [24]. Ratings were implemented on a 6-point quantitative index.

The EuroQol Questionnaire EQ 5D 5L is a standardized patient reported measure for health to support clinical and health economic appraisal [24]. Subjects' self-ratings in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a five-point Likert scale are mapped on a society-specific utility rating. The instrument provides a subjective as well as societal perspective on the individuals' health ratings. The derived health utilities support the calculation of Quality Adjusted Life Years, an often-used health economic measure.

The electrode garment

The 58 polymer rubber electrodes in the suit are connected to the control unit and operate in pairs. Each pair of an anode and a cathode is situated at a dermatome of a target muscle group.

The individual stimulation is programmed by a certified clinician. The clinician identifies the muscular regions (agonists) which most prominently limit the intended functional movements. Stimulation patterns can be selected from 30 pre-defined default settings and individually adjusted. If the movement disorder is accompanied by pain, all electrode multisite stimulation is activated in addition. The stimulation pattern activates the electrode pairs sequentially in an interleave mode. The stimulation intensity is selected based on subjects' weight, height and severity of the symptoms and readjusted if the stimulation sensation (if any) is conceived uncomfortable. The clinician shall ensure that stimulation intensity remains below motor threshold. The stimulation is delivered continuously at 20 Hz for the set time period. The stimulation remains unaltered throughout the entire application session, an adaptation by the patient is not possible.

Stimuli are voltage controlled with a constant amplitude of 20 V, stimulation intensity is adjusted via pulse width up to a maximum of 170 µs, current is limited at 46 mA. Maximum pulse energy is limited to 300 mJ. Electrode locations and respective motoric functions are indicated in Figure 1.

Power supply is provided by 4 AAA batteries. All safety standards as given for nerve and muscle stimulators by IEC 60601-2-10 are observed. We did not observe any adverse events in this investigation.

Assessments were carried out upon evaluation of the subject's physical status, considering and avoiding fatigue from test procedures or any other avoidable strain on the testee as far as possible. Assessors were certified clinical coaches for Exopulse and experienced in the conduct of the assessments described here. The first assessment (T0) was scheduled prior to the first stimulation with the EXOPULSE Mollii Suit. The testee was asked to already wear the suit at all assessments as well as any aid (primarily orthotics) he or she uses during daily living. The second assessment (T1) followed immediately after 60 min of stimulation. The third assessment followed a 4-week trial period, with the participant being asked to schedule a last stimulation session on the day before returning the trial suit. Participants were recommended to use the suit for 60 min on every second day during the entire trial period. Subjects were informed that no change of lifestyle, routine, or other

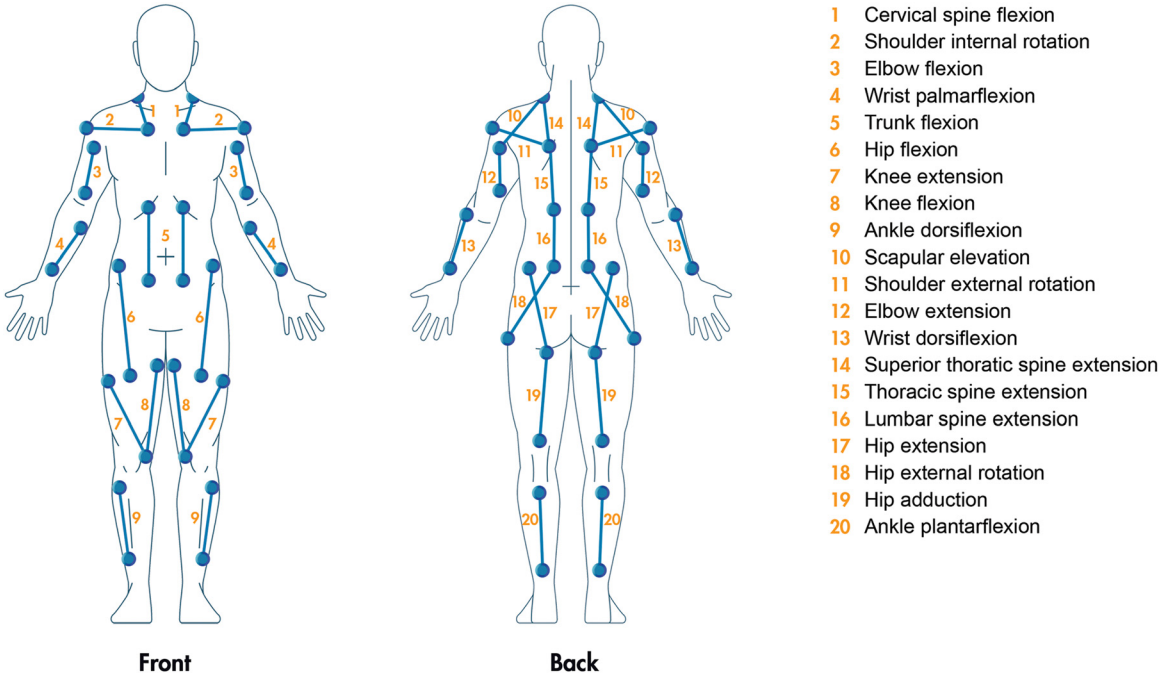


Figure 1: Exopulse Mollii Suit electrode positions and respective motoric functions are indicated. The maximum distance between a pair of active electrodes is dependent of the suit size, ranging from 23 cm in the smallest to 38 cm in the largest sizes. The electrodes are 3×3 cm^2 in the children and 4×4 cm^2 in the adult suit sizes.

applied medical interventions, e.g., physical therapy, should be made during their participation in the study.

Statistical analyses

The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to test for normality. As data were not normally distributed, changes over time were assessed by applying a Friedman Test. Pairwise changes were assessed by a Durbin-Conover Test with applied Bonferroni correction. Cohen's d was applied to estimate the overall effect size between T0 and T2. Cohen's d is interpreted to exhibit a small or no effect in below 0.3, a medium effect if 0.3≤d≤ 0.8 and big if d exceeds 0.8. Data collection was performed in a Lime Survey (Limesurvey GmbH, Hamburg, Germany http://www.limesurvey.org) version adopted to the needs of clinical data collection. Analysis was conducted using R version 4.1.3 [26].

Data were stratified for analysis by etiology. Further, the data were stratified for subjects having an entry BBS score<45 indicating an increased risk of falling. We also stratified the data regarding CP to elucidate the performance in the adult and pediatric population.

Results

Data from 72 testees were retrieved from a total of 7 certified orthotic workshops. The convenience sample spanned infantile cerebral palsy (n=29), multiple sclerosis (n=23) and stroke (n=20) as leading etiologies. All participants completed T2, however, not all measurements were completed by all subjects. Non-completion was reported to may have been due to subjects' exhaustion, loss of concentration and time constraints. No information is available allowing to judge subjects' compliance with the manufacturer's recommendations.

The demographic information of the test cohort is shown in Table 1.

In the following tables significance levels of the paired tests are indicated by *: p<0.05, **: p<0.01, *** p<0.001, (t): p<0.1. Non-annotated differences do not exhibit statistical significance. The BBS, FGA and WMFT results are presented as scores. The results of TUG are shown in seconds (s), the results of the 10 m walk test are shown as velocity (meters per seconds). For EQ-5D-5L the utility value is shown. All values refer to the mean. The standard deviation (STD) is presented in the respective units. The column "Friedman" indicates the significance of the Friedman test. The effect size (Cohen's d) is reported in relation to T0. The number of subjects is indicated by N.

Table 1: Demographics of subjects included in analysis. F, female; M, male.

	All subjects	All subjects (BBS<45)	ICP (BBS<45)	MS (BBS<45)	Stroke (BBS<45)
n	72	44	16	16	12
Age	36.64 (19.8)	39.16 (19.9)	20.38 (10.6)	50.13 (9.7)	49.58 (21.3)
Gender	F=44, M=28	F=24, M=20	F=7, M=9	F=13, M=3	F=4, M=8
GMFCS at T0	1–3	1–3	1–3	1–3	1–3

Tables 2a–c show the assessment results for the subpopulations with CP, MS and stroke, respectively. The analysis is stratified to subjects with a BBS score below 45 at T0. Table 3 shows the mean differences and effect sizes of all participants, i.e. no stratification for the BBS score was implemented.

In the real-world setting, individual subjects' improvement manifested itself most prominently in the Berg Balance Scale. This is observed in the entire cohort both independent of the etiology and of the stratification for increased risk of falling. The effect sizes exceed 0.8 in all investigated scenarios and may hence be classified as large.

We will visualize the BBS assessments for the CP, MS and stroke subgroup in Figure 2A–C, respectively.

The improvement in the FGA is of comparable magnitude for subjects with CP and MS. The FGA was found to be exhausting in many subjects presented with stroke as leading etiology and hence was conducted in six participants only. The TUG captured subjects' improvements in the stroke subgroup and in subjects with multiple sclerosis. In the CP cohort the effect sizes were small with significance being only reached in the overall group. The 10mWT captured subjects` improvements in the multiple sclerosis subgroup with large effect size. The results in the CP and the stroke subgroup exhibit significance with moderate and large effect sizes respectively.

Table 4 presents a distinction between the adult and pediatric CP subjects.

While statistically significant differences in the children subgroup can be detected with the BBS, no other outcome exhibits significance in this small group. The similarity of the effect sizes when compared to the adult group may be noted.

Upper extremity motor function improvements measured by the Wolf Motor Function test can be detected in the CP and the MS cohort. The test remains insensitive in the stroke cohort. The effect is more prominent in the adult CP subjects and trending may be indicated with the children's population.

Table 5 presents the impact of the intervention on spasticity-related pain. Subjects were stratified as to whether they denoted a minimum level of pain on the respective EQ 5D 5L pain subscale.

The results are visualized in Figure 3A–C respectively.

Table 2a: Assessment results of the CP subpopulation for testees with a BBS score below 45 at T0. For annotations, please refer to the general description of the table structure at the beginning of the results section. Effect sizes are statistically significant and large for BBS, FGA and WMFT and medium for the 10mWt and EQ5D5L. The TUG exhibits a small or no effect.

Outcome	n	T0, STD	T1, STD	T2, STD	Δ(T0–T1)	Δ(T0–T2)	Friedman	Cohen's d
BBS	16	31 (13.2)	36.3(14.1)	39.1 (15.3)	5.25***	8.06***	***	1.64
TUG	16	26.4 (26.0)	22.0 (19.7)	23.2 (27.9)	−4.4	−3.2*	*	0.29
FGA	13	11 (5.5)	15.5 (7.6)	16.6(7.6)	4.5***	5.6***	***	1.59
10mWT	15	0.96 (0.46)	1.0 (0.33)	1.1 (0.4)	0.05	0.1 (t)	*	0.76
WMFT	9	53.1 (19.4)	56.1(19.3)	59.1 (18.9)	3.0 (t)	6.0***	**	1.00
EQ 5D 5L	15	0.76 (0.2)	0.87 (0.1)	0.87 (0.1)	0.109 (t)	0.112*	*	0.50

Table 2b: Assessment results of the MS subpopulation for testees with a BBS score below 45 at T0. For annotations, please refer to the general description of the table structure at the beginning of the results section. All outcomes exhibit statistically significant large effect sizes.

Outcome	n	T0, STD	T1, STD	T2, STD	Δ(T0–T1)	Δ(T0–T2)	Friedman	Cohen's d
BBS	15	27.8 (13.0)	34.1 (14.4)	38.1 (12.3)	6.28**	10.33***	***	1.83
TUG	14	29.7 (20.6)	23.3 (14.8)	21.3 (11.8)	−6.40***	−8.36***	***	0.83
FGA	6	11.3(2.3)	16.7 (4.4)	18.3 (7.0)	5.3*	7.0**	*	1.28
10mWT	11	0.66 (0.34)	0.76 (0.34)	0.80 (0.32)	0.098**	0.145***	**	1.07
WMFT	6	64.2 (11.7)	71.7 (4.37)	71.7 (5.1)	7.5*	7.5*	*	0.93
EQ 5D 5L	14	0.55 (0.27)	0.77 (0.10)	0.73 (0.21)	0.22***	0.177**	***	1.11

Table 2c: Assessment results of the stroke subpopulation for testees with a BBS score below 45 at T0. For annotations, please refer to the general description of the table structure at the beginning of the results section. Effect sizes are statistically significant and large for BBS, 10mWT and EQ5D5L. A statistically significant medium effect is seen with TUG. The effect observed with FGA is not statistically significant, the low number testees having finished this test may be noted. Also, WMFT does not exhibit statistical significance.

Outcome	n	T0, STD	T1, STD	T2, STD	Δ(T0–T1)	Δ(T0–T2)	Friedman	Cohen's d
BBS	12	34.7(8.4)	40.8(8.6)	41.6(8.3)	6.08***	6.92***	**	1.28
TUG	12	36.0 (27.22)	25.7(20.5)	22.3 (15.7)	−10.32***	−13.66**	**	0.78
FGA	6	14.17 (11.22)	16.5 (12.0)	19 (8.9)	2.33	4.83	(t)	0.89
10mWT	11	0.57 (0.32)	0.67 (0.33)	0.76 (0.35)	0.096	0.19**	*	0.92
WMFT	8	28.6(24.1)	30.6 (23.8)	38.3 (28.6)	2.00	9.63		0.71
EQ 5D 5L	10	0.54 (0.30)	0.66 (0.23)	0.75 (0.24)	0.13	0.21*	*	1.26

The structure and terminology of the tables are described in the text. The significance levels of the paired tests are indicated by *p<0.05, **p<0.01, ***p<0.001, (t): p<0.1.

Table 3: Mean differences and effect sizes for the unstratified cohort. For annotations, please refer to the general description of the table structure at the beginning of the results section. Large statistically significant effect sizes are exhibited by the BBS in all three etiologies indicating the specific sensitivity of this instrument for the effects investigated. The effect sizes are smaller than those in the stratified groups, indicating the ceiling of the instrument. FGA exhibits large statistically effect sizes for CP and MS. Apart from EQ5D5L all other outcomes exhibit statistically significant effects of medium size.

All cohort (n=72)	CP		MS		Stroke	
Outcome	ΔT0–T2	Cohen's d	ΔT0–T2	Cohen's d	ΔT0–T2	Cohen's d
BBS	5.92*** (n=25)	1.161	8.24*** (n=21)	1.377	5.6*** (n=20)	1.184
TUG	−3.2*** (n=27)	0.369	−5.93*** (n=21)	0.67	−8.55** (n=20)	0.572
FGA	4.86*** (n=22)	1.543	6.25*** (n=12)	1.349	3.86** (n=14)	0.783
10mWT	0.11* (n=26)	0.562	0.166*** (n=18)	0.991	0.16** (n=19)	0.721
WMFT	5.72*** (n=18)	0.795	4.6* (n=10)	0.647	7.19* (n=16)	0.727
EQ 5D 5L	0.11** (n=27)	0.538	0.08 (t) (n=21)	0.337	0.13* (n=17)	0.776

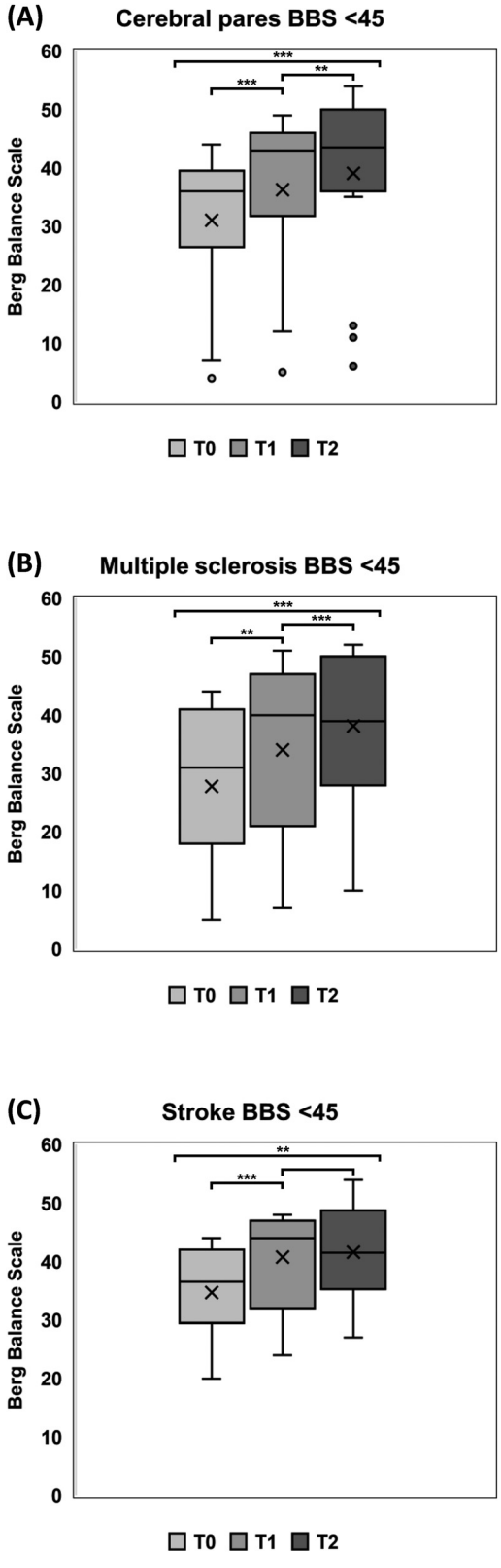


Figure 2A–C: Change in Berg Balance Scale (BBS) scores in patients with (A) cerebral palsy, n=16, (B) multiple sclerosis, n=15 or (C) stroke, n=12. Measurements were taken at three different timepoints – baseline (T0), after the first 60 min stimulation session (T1) and after four of weeks intervention (T2). All subjects had an BBS entry score of <45 at baseline.

Discussion

The results indicate significant improvements in static and dynamic balance as well as in ambulation performance. For the first time, it is also possible to show the effect in a cohort of subjects suffering from multiple sclerosis.

The effects are most pronounced in the BBS. Large effects of high statistical significance are observed for all etiologies presented here. We stratified for individuals with BBS/PBS<45 to investigate subjects with an increased risk of falling (Tables 2a–c). Absolute BBS values increase with the mean value approaching or crossing (stroke) the threshold value of 40. Comparing these results to that of the entire cohort (Table 3) we find effects to be more pronounced in all three etiologies. Within the CP group the effects seem to be of similar magnitude for children and adults.

Palmcrantz et al. [18] had reported a non-significant (p=0.063) change in BBS median score by 3.5 points and no changes in timed walking tests. By comparison, Ng et al. [27] report an increase of BBS scores due to TENS stimulation combined with intensive task-oriented balance training in a subacute stroke population of d=1.4 (calculated after Ng et al., p<0.01).

The improvements seen in the BBS/PBS seem to match or exceed the results achieved in standard rehabilitation programs for CP using intensive upper and lower extremity training, treadmill training [28] or procedures including gaming balance boards [29]. Here, average improvements between 2 and 6 points were reported. A further standard procedure for such patients includes postural insoles, where a median core of improvement of 2 is reported after 3 months with no immediate effect visible [30].

In addition to the results resembling static balance (BBS/PBS), similar effect sizes can be observed with the FGA indicating dynamic balance. However, as the FGA requires a higher degree of independent walking and may be more exhausting to the testee, not all subjects underwent this assessment. Raffalt et al. report an alteration of non-linear dynamics during walking in children with unilateral CP after 24 weeks of Exopulse Mollii Suit treatment [31]. They conclude that the temporal structure of the trunk acceleration in the anterior-posterior direction was altered towards that of healthy individuals.

TUG and 10mWT are instruments more widely used in clinical routine. With the TUG we see only small effects in the CP population. We calculate the effect size from the data reported by Bakaniene et al. [16] in CP children and obtain d=0.42 with no possibility to assess significance. Thus, our findings seem to be in alignment with their results. No such change was observed by Ertzgaard et al. [15] in their mixed

Table 4: Absolute differences and effect sizes for CP children and adults in subjects with BBS<45. For annotations, please refer to the general description of the table structure at the beginning of the results section.

BBS<45	CP children	CP children		CP adults		
Outcome	N	ΔT0-T2	Cohen's d	N	ΔT0-T2	Cohen's d
BBS	7	6.86[a]	1.49	9	9[b]	1.72
TUG	7	−1.47	0.37	9	−4.6[a]	0.31
FGA	4	4.00 (t)	2.83	9	6.36[b]	1.58
10mWT	7	0.22 (t)	0.87	8	0.121	0.63
WMFT	4	6.75	0.74	5	5.4[b]	1.73
EQ 5D 5L	6	0.12	0.80	9	0.11	0.40

Table 5: Absolute differences and effect sizes for subjects reporting pain at T0. For annotations, please refer to the general description of the table structure at the beginning of the results section.

Etiology	n	T0, STD	ΔT0–T1	ΔT0–T2	Cohen's d
CP	14	2.79 (0.70)	−0.57**	−1.00***	1.28
MS	16	3.06 (1.00)	−1.06***	−0.81**	0.78
Stroke	12	2.58 (0.9)	−0.75*	−0.75*	0.78

population in the PP analysis. The effects seen in the current investigation in the MS and stroke cohort are substantially larger. Arkkukangas et al. [32] did not observe changes in TUG in seven single cases of CP-children including GMFCS levels 1 to 4.

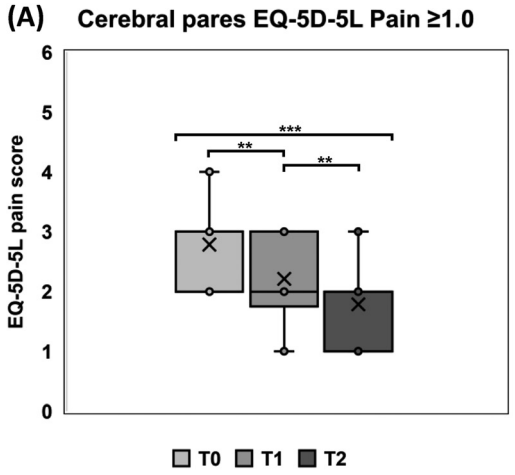
The 10mWT shows mean effect sizes ranging from 0.76 to 1.07 in this investigation. Ertzgaard et al. [15] had reported that the PP analysis showed a reduction of comfortable gait time by –1.5 s (p=0.026) during stimulation in a 10 m walking test in their mixed population. These results do not contradict each other.

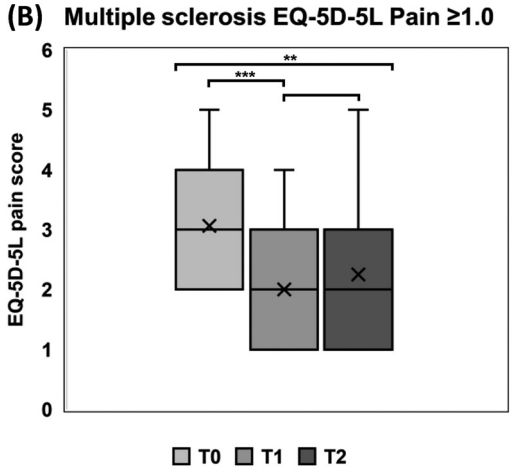
Ertzgaard et al. [15] investigated functional effects on the upper extremity using both the ARAT and the WMFT. Both measures remained insensitive in the data reflecting the ITT analysis. Palmcrantz et al. [18] report statistically significant changes in ARAT total score, but with apparently very low effect size. This result is contrasted by Palmcrantz et al. [18] reporting a substantial increase in the median of the hand function item of the stroke impact scale, which, however, remained statistically insignificant.

The utility values derived from the EuroQol 5 Dimensions 5 Level instrument exceed an absolute value of 0.1 in all cohorts. The effect is most pronounced in the stroke cohort. In the CP cohort, the effect is more prominent in the pediatric population. In the CP adult cohort, the effect does not exhibit statistical significance. Overall, these results are particularly encouraging. Utility values are the basis for informing on possible cost-effectiveness effects. Recent modelling by Kuhlmann et al. [33] specifically paying attention to the effects of reducing fall risk and associated utility changes indicates cost effectiveness with regard to microprocessor-controlled exo-prosthetic knee joints. No such investigations exist for electrode garments. However, the size of utility changes and the overall cost base make a favorable evaluation seem possible.

Spasticity in the investigated cohort is associated with pain in most of the subjects. We observed a significant decrease in all three subgroups described. It should be acknowledged that the derivation from EQ 5D 5L pain subscale is a comparatively coarse instrument and may suggest that these findings pose lower limits to the effect of pain reduction. Our results are in contrast with the findings of Ertzgaard et al. [15], where changes in pain assessment remain insensitive, and with the results of Palmcrantz et al. [18], where pain was assessed by the respective Fugl-Meyer sub scores for upper and lower extremity. The results here support earlier findings by Riachi et al. [34].

The results presented here were both instantaneous and sustained over the period of assessment. Statistically significant changes of substantial magnitude are observed at T1 and maintained until T2. To some extent this may be in contrast with recent findings of Pennati et al. [19], where immediate measurements of wrist spasticity as assessed by the Neuroflexor (Aggero Med-Tech AB, Älta, Sweden) [35] instrument as well as assessments with the modified Ashworth scale did not show sensitive effects.





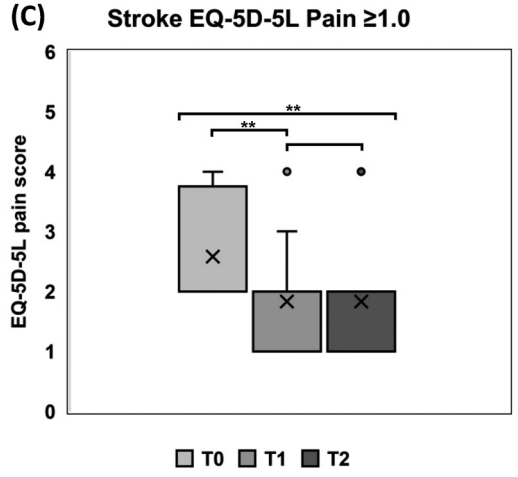


Figure 3A–C: Changes in EQ-5D-5L pain scores in patients with (A) cerebral palsy, n=14, (B) multiple sclerosis and (C) stroke at baseline (T0), after the first 60 min stimulation session (T1) and after four weeks of intervention (T2). All subjects had an EQ-5D-5L pain entry score of >1 at baseline.

Nonetheless, effect sizes reported here as well as the overall response to the therapeutic intervention are encouraging and in contrast with some of the earlier findings. This may be due to our more stringent subject selection. We solely selected walkers and limited the investigation to subjects cognitively able to follow instructions. It seems plausible that the first may have increased the sensitivity to ambulation related outcomes while the latter may have helped to increase compliance. Technical advances as well as an adaptation of stimulation patterns may have increased individual responsiveness.

Limitations

This work presents preliminary data collected in a real-world environment supporting trial fittings for commercial purposes. As such, neither can bias be excluded nor have group effects been subject to comparison. The samples are small and therefore the generalization of the results is limited.

The outcomes used and investigated in this project are well established in rehabilitation. However, the psychometric properties have not fully been investigated for all etiologies and ages reported about in the investigation. The interpretation of such results requires clinical judgement.

The results presented here focus on the assessment of functional clinical effects. Earlier work focused on the direct measurement of a reduction in spasticity as well as on effects on joint movements. While some effects could be revealed by the Neuroflexor instruments, clinical instruments such as the Ashworth or the Tardieu scale were not able to show effects, possibly due to their coarseness. Results reported on joint movements were positive, as reported by Flodstroem et al. [20] and Hedin et al. [17]. Overall, while effects reported earlier remain small on group level, the large inter-individual variability was often hinted to.

Conclusions

Individualized multi-site transcutaneous electrical stimulation seems to increase ambulation-related skills in subjects with upper motor neuron syndrome stemming from infantile cerebral palsy, multiple sclerosis, and stroke. These results obtained with an improved full-body electrostimulation garment show encouraging effects on static and dynamic balance, fall risk and mobility. Upper extremity improvement may be observed as well as an overall increase in health utility and a reduction in spasticity-related pain. Effects are immediate (after 1 h of stimulation) as well as sustained (1 month of application)

with stimulation applied for 60 min daily or every other day. Outcomes being sensitive to such improvements could be identified. The results may improve the quality of individual trial fittings as well as inform controlled trials that are most clearly warranted in this context.

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Ethical approval: Retrospective data analysis was approved by the ethics board of the University of Göttingen.

Informed consent: Informed consent was obtained from all individuals included in this investigation.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: AH, SM and AS are full time employees within the Ottobock company group. Ottobock is the owner of Exoneural Network AB. ME and MWe are full time employees of Exoneural Network AB, the manufacturer of the full body garment investigated. WM is contracted for the Medical Advisory Board of Exoneural Network AB. GdC and FB are not reporting a conflict of interest.

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Appendix

The data presented specifically in Tables 2a–c and 5 are non-normally distributed. Mean and standard deviation were presented as we chose to lay focus on the characterization of the effects by Cohen's d. We display the relevant data of the boxplots to allow a higher degree of legibility in Tables A1–A4. Please do also refer to the general description of the table structure at the beginning of the results section.

Table A1: Median, Range and Quartil data for CP subjects with BBS<45 at T0, T1 and T2.

Outcome	T0 Median Range	T0 Quartil 1 Quartil 3	T1 Median Range	T1 Quartil 1 Quartil 3	T2 Median Range	T2 Quartil 1 Quartil 3
BBS	36	27.5	43	33.25	43.5	38
	4–44	38.5	5–49	46	6–54	50
TUG	15.88	12.2	14.00	11.65	13.40	11.44
	8–102	22.61	7.3–82.3	21.90	8.4–120	18.24
FGA	10	8	15	10	17	12
	0–19	16	1–27	23	0–27	21
10mWT	0.83	0.76	0.95	0.87	1.02	0.90
	0.27–2.07	0.93	0.31–1.88	1.08	0.27–2.14	1.30
WMFT	50	44	60	48	68	53
	13–75	68	15–75	71	17–75	72
EQ 5D 5L	0.82	0.74	0.87	0.83	0.87	0.82
	0.21–1.00	0.87	0.76–1.0	0.91	0.72–1	0.92

Table A2: Median, Range and Quartil data for MS subjects with BBS<45 at T0, T1 and T2.

Outcome	T0 Median Range	T0 Quartil 1 Quartil 3	T1 Median Range	T1 Quartil 1 Quartil 3	T2 Median Range	T1 Quartil 1 Quartil 3
BBS	31	19.5	40	21.5	39	29
	5–44	39.5	7–51	45	10–52	48
TUG	24.1	16.66	19.18	14.16	18.2	13.31
	10.2–77.5	30.14	9.3–66.5	26.83	8.49–52	24.86
FGA	11	11	15.5	15	19	13.5
	8–15	11.75	11–24	18.25	9–28	22.25
10mWT	0.50	0.37	0.72	0.46	0.85	0.48
	0.3–1.2	0.90	0.28–1.2	1.03	0.37–1.21	1.06
WMFT	65	55.25	73	70.25	74	70.75
	50–75	74.75	64–75	75	62–75	75
EQ 5D 5L	0.59	0.42	0.78	0.70	0.81	0.71
	0.05–0.89	0.74	0.62–0.94	0.81	0.24–0.97	0.82
EQ5D 5L	2.5	2	1	1	1	1
PAIN	1–5	3.75	1–3	2	1–4	2.75

Table A3: Median, Range and Quartil data for stroke subjects with BBS<45 at T0, T1 and T2.

Outcome	T0 Median Range	T0 Quartil 1 Quartil 3	T1 Median Range	T1 Quartil 1 Quartil 3	T2 Median Range	T2 Quartil 1 Quartil 3
BBS	36.5	30.5	44	38	41.5	37.75
	20–44	42	24–48	47	27–54	48.25
TUG	23.15	17.13	16.63	13.55	16.75	12.76
	10.5–2.2	45.29	8–77.5	36.69	7.5–63	31.56
FGA	12.5	6.75	16.5	8.75	19.5	12.25
	0–28	23.5	0–30	26.5	8–28	26.75
10mWT	0.52	0.32	0.72	0.35	0.81	0.54
	0.13–1.11	0.78	0.13–1.09	0.92	0.16–1.27	0.99
WMFT	19	13.5	23.5	14.25	40	11.25
	3–75	39.25	3–75	44–75	3–75	59.75
EQ 5D 5L	0.62	0.38	0.74	0.69	0.82	0.76
	−0.09-0-8	0.78	0.21–0.89	0.79	0.13–0.96	0.88
EQ5D 5L	2	2	1.5	1	2	1
PAIN	1–4	3.75	1–4	2	1–4	2

Table A4: Median, Range and Quartil data for subjects exhibiting pain at T0 at T0, T1 and T2.

EQ5D 5L PAIN	T0 Median Range	T0 Quartil 1 Quartil 3	T1 Median Range	T1 Quartil 1 Quartil 3	T2 Median Rrange	T2 Quartil 1 Quartil 3
CP	3	2	2	2	2	1
	2–4	3	1–3	3	1–3	2
MS	3	2	2	1	3	1
	2–5	4	1–4	3	1–5	3.5
Stroke	2	2	2	1.5	2	2
	2–4	2.5	1–4	2.5	1–4	2

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