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Children with cerebral palsy: a systematic review and meta-analysis on gait and electrical stimulation

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Objective: To conduct a systematic review and meta-analysis using the International Classification of Functioning to determine the summary effect of electrical stimulation on impairment and activity limitations relevant to gait problems of children with cerebral palsy.
Methods: We identified 40 cerebral palsy and electrical stimulation studies, and 17 gait studies qualified for inclusion. Applying enablement classification methods to walking abnormalities created two subgroups: impairment ($N = 14$) and activity limitations ($N = 15$). Overall, 238 participants experienced electrical stimulation treatments and 224 served as a no stimulation control group. Calculations followed conventional data extraction and meta-analysis techniques: (a) individual standardized mean differences, (b) summary effect size, (c) I^2 heterogeneity test, (d) fail-safe N analysis and (e) moderator variable analyses.
Results: Common outcome measures associated with impairment ($n = 3$) and activity limitations ($n = 6$) were submitted to separate random effects models meta-analyses, and revealed significant cumulative effect sizes: (a) impairment = 0.616 (SE = 0.10) and (b) activity limitations = 0.635 (SE = 0.14). I^2 indicated low and medium amounts of dispersion, whereas fail-safe analyses revealed high N-values for both disablement categories. Moderator variable analyses further confirmed the positive treatment effects from both functional and neuromuscular stimulation.
Conclusions: The present systematic review and meta-analyses determined medium effect sizes for electrical stimulation on walking impairment and activity limitations of children with cerebral palsy.

Introduction

Cerebral palsy is the most common paediatric neurological disorder in the United States, affecting between two and five children per thousand births.[1,2] The cost of care for individuals with cerebral palsy is estimated at about US$8.2 billion in the USA alone.[3,4] A considerable amount of the cost of care involves gait abnormalities. A useful way to categorize gait problems is through the International Classification of Functioning. In this study, we investigated two categories – impairments and activity limitations. The need to treat the high frequency of walking problems that characterize many children with cerebral palsy remains a major challenge. However, consistent findings on effective gait interventions that minimize

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impairments and activity limitations are elusive, primarily because of methodological difficulties and a limited numbers of subjects.

One minimally invasive technique, electrical stimulation, shows promise for improving walking capabilities, but the evidence is difficult to interpret given the different types of electrical stimulation available (i.e. functional, neuromuscular, and therapeutic) as well as the broad cerebral palsy presentations with multiple goals to improve gait.[5] Indeed, even in a particular type of electrical stimulation, to achieve the same treatment goals, methodologies differ by location, intensity and length of treatment times. Furthermore, patients with cerebral palsy show a great deal of heterogeneity (e.g. diplegia, hemiplegia, athetoid gait, and spastic gait, all with more or less severe symptoms).

While there have been some consistent and potentially profound walking effects of functional electrical stimulation on the gastrocnemius-soleus muscles during locomotion to bring about short- and long-term benefits from minimizing body function (or structure) impairments and increasing capabilities for executing actions, the data are still largely clinical and anecdotal.[6–9] Furthermore, these results are overshadowed by studies that rely heavily on subjective reports, and small numbers of participants.[10–15] For example, in one of the largest studies involving stimulation of the peroneal nerve of 120 children conducted over a six-year period, Gracanin *et al*. claimed improvements in the leg movement patterns of some children, although no data were provided and no statistical analyses were performed.[11] In contrast, a sample of children with either hemiplegia or diplegia who were treated using stimulation of the peroneal nerve failed to show consistent changes in gait performance in five of the seven children.

These inconsistent gait findings clearly indicate a need for a systematic review and meta-analysis. Indeed, investigating cerebral palsy and electrical stimulation studies that focus on gait impairments and activity limitations will increase our understanding about effective treatments. Moreover, this systematic review and meta-analysis comes at a critical time because of the increasing potential for invasive techniques via implanted electrodes in paediatric cerebral palsy patients.[16,17]

Methods

Over 30 years ago, Glass formally introduced the statistical technique called meta-analysis.[18,19] Two stated purposes of a structured meta-analysis are integrating findings from multiple studies and conducting a quantitative analysis of findings.[18–20] Our systematic review and meta-analyses were consistent with recommended conventional techniques.

Electrical stimulation types: three operational definitions

Our meta-analysis focused on three primary types of electrical stimulation used to modify impairments and activity limitations in children with cerebral palsy. Functional stimulation is defined as surface electrical stimulation to muscles and/or nerves that have impaired motor control for the purpose of overcoming an inability to contract and execute functionally useful movements.[21] Neuromuscular stimulation is defined as surface electrical stimulation to muscles that is usually high in intensity and short in duration for the purpose of initiating a contraction and subsequent movement.[22] Therapeutic stimulation is defined as electrical stimulation with low intensity (subthreshold levels) that may be applied continuously for a long duration.[23]

Structured review: study selection and inclusion/exclusion criteria

An exhaustive search for cerebral palsy, gait and electrical stimulation articles focused on six computerized databases (1980–November 2009; strategy is available on request): (a) PubMed, (b) Cochrane Database of Systematic Reviews, (c) EMBASE, (d) Web of Science, (e) PEDRO and (f) CINAHL. Key search words included cerebral palsy, electrical stimulation, electromyography triggered stimulation, functional electrical stimulation, neuromuscular electrical stimulation, therapeutic electrical stimulation, impairment, activity limitations, gait, and walking. Supplementary search techniques included examining reference lists of retrieved articles. Our initial literature search identified 40 full-length cerebral palsy, gait and electrical stimulation articles.[5–10,14,21–52]

Four a priori inclusion and exclusion criteria follow:

- The first exclusion criterion concerned the nature of the study with an electrical stimulation treatment for walking impairments and activity limitations of children with cerebral palsy. Literature reviews and case studies without quantitative group data for individual studies did not qualify for inclusion. Consequently, 11 studies were excluded.[8,9,36,38,40,42–45,52–53]
- The second exclusion criterion focused on the legs and gait patterns. Seven studies involving either the arms or the trunk were excluded.[6,32,34,36,39,47,48]
- A third exclusion criterion involved reliability articles and insufficient data required for extraction. Four articles were excluded based on this criterion.[5,10,33,41]
- The final inclusion and exclusion criterion involved the three dominant types of electrical stimulation. However, one study administered a unique type of electrical stimulation known as microcurrent. To minimize between-subject variability in our meta-analysis and increase precision, we decided not to include the one microcurrent electrical stimulation study.[28]

The 17 remaining studies were included for data extraction. Noteworthy, each of the studies used one of three types of electrical stimulation during protocols across several sessions as an intervention for treating cerebral palsy gait deficits.[9,14,21–27,29–31,38,46,49–51] Tables 1–3 provide specific details about each study including cerebral palsy type, treatment protocols, treatment or intervention goals and quality assessment. Two authors applied the selection criteria (JC and SN), and

Table 1 Characteristics of the cerebral palsy and electrical stimulation studies used in the present meta-analysis

Study	Total *N*	Mean age (years)	Cerebral palsy type	Primary treatment goal
Comeaux *et al.*, 1997[9]	14	9.14	10 Diplegia 4 Hemiplegia	Improve gait: dorsiflexion at heel strike
Dali *et al.*, 2002[23]	82	10.92	32 Diplegia 25 Hemiplegia	Improve motor function
Durham *et al.*, 2004[49]	10	9.5	0 Diplegia 10 Hemiplegia	Improve asymmetrical walking/gait
Hazlewood *et al.*, 1994[51]	20	8.67	0 Diplegia 20 Hemiplegia	Improve gait by stretching for > range of motion
Ho *et al.*, 2006[38a]	13	7.57	5 Diplegia 4 Hemiplegia	Improve gait
Jeronimo *et al.*, 2007[31]	10	4.6	5 Hemiplegia	Improve gait
Johnston *et al.*, 2004[50]	17	8.35	13 Diplegia 4 Quadriplegia	Augment walking/gait
Katz *et al.*, 2008[24b]	7	3.3	4 Diplegia 1 Hemiplegia	Improve motor function
Kerr *et al.*, 2006[22]	63	11	55 Diplegia 1 Quadriplegia 1 Dystonia 1 Ataxia 2 Non-Classifiable	Improve strength
Khalili *et al.*, 2008[30]	11	12.8	11 Diplegia	Improve motor function
Maenpaa *et al.*, 2004[29]	17	6.42	6 Diplegia 11 Hemiplegia	Improve range of motion
Nunes *et al.*, 2008[27]	10	11.34	10 Hemiplegia	Improve range of motion and strength
Sommerfelt *et al.*, 2001[25]	16	8.69	12 Diplegia 0 Hemiplegia	Improve ambulation and muscle strength
Stackhouse *et al.*, 2007[26]	12	10.51	11 Diplegia	Improve gait and force production
Steinbok *et al.*, 1997[14]	44	7.21	44 Diplegia 0 Hemiplegia	Improve motor function
van der Linden *et al.*, 2003[46]	22	8.5	14 Diplegia 7 Hemiplegia 1 Quadriplegia	Improve motor function, strength and gait
van der Linden *et al.*, 2008[21]	18	8	6 Diplegia 6 Hemiplegia 2 Monoplegia	Therapeutic effects of functional stimulation on gait

Studies are listed in alphabetical order.
[a]Tested 13 cerebral palsy subjects and 6 healthy subjects.
[b]Tested 7 cerebral palsy subjects and 6 healthy subjects.

Table 2 Electrical stimulation treatment characteristics (i.e. parameters, duration, frequency and intensity), sessions, total minutes and treatment protocol for individual studies

Study	Electrical stimulation parameters: duration, frequency and intensity for one session	Treatment sessions	Treatment duration: total minutes	Treatment protocol
Comeaux *et al.*, 1997[9]	32 Hz stimulation; 0.5 s onset; amplitude turned slowly until visible contraction observed; in comfort range for 15 min	Daily for 4 weeks	840	Neuromuscular stimulation
Dali *et al.*, 2002[23]	35 Hz stimulation; pulse amplitude 1–5μA; 360 min	6 nights/ week for 12 months	103 680	Therapeutic stimulation
Durham *et al.*, 2004[49]	40 Hz stimulation; pulse width 3 to 350μs and ramp of 0–4 s; intensity 15–100 mA	12 weeks	Not specified	Functional stimulation
Hazlewood *et al.*, 1994[51]	30 Hz stimulation; pulse width 100μs; 2 s rise time and 15 s off; 60 min duration	35 days	2 100	Therapeutic stimulation
Ho *et al.*, 2006[38]	32 Hz stimulation; ramp time of 0.2 s and pulse duration of 300μs; amplitude 10–40 mA; 15 trials/session	2 sessions	30 trials	Functional stimulation
Jeronimo *et al.*, 2007[31]	40 Hz biphasic, symmetric current with pulse-width of 250 ms; on:off time: 6:12 s	12 sessions	300	Functional stimulation
Johnston *et al.*, 2004[50]	Balanced, asymmetric waveform; 20 Hz; amplitude 20 mA; stimulated exercises; ramp up 3 s; ramp down 1–2 s; pulse duration 200 μs; 3 sets 10 repetitions; walking	5 Days/week for 4 weeks (exercise phase)	Not specified	Percutaneous intramuscular functional stimulation
Katz *et al.*, 2008[24]	20 Hz stimulation, pulse-width 0.25 ms constant current; intensity 1–5 mA	Daily for 3 months	2 520	Electrical stimulation
Kerr *et al.*, 2006[22]	35 Hz stimulation; pulse duration 300 ms; on:off time 7 : 12 s; ramp up 2 s; ramp down 1 s; NMES: 60 min at highest intensity tolerated; TES: 480 min at sensory threshold level <10 mA	5 days/week for 16 weeks	4 800 (NMES) 38 400 (TES)	Neuromuscular stimulation and therapeutic stimulation
Khalili *et al.*, 2008[30]	30 Hz stimulation; pulse-width 0.4 ms; on : off time 4 : 4 s; ramp up 0.5 s	3 times/week for 4 weeks	360	Electrical stimulation
Maenpaa *et al.*, 2004[29]	10–20 Hz stimulation at sensory threshold; pulse duration 300 ms; intensity ranged from 4 to 20 mA; on : off time 1 : 1 s	8 times	256	Neuromuscular stimulation
Nunes *et al.*, 2008[27]	50 Hz; pulse-width 250μs stimulation; current intensity 28–44 mA; on:off time 5 : 10 s	Group 1: 14 sessions Group 2: 7 sessions	420 210	Neuromuscular stimulation
Sommerfelt *et al.*, 2001[25]	40 Hz stimulation; intensity <10 mA; pulse-width 300 μs; duration 300 min	6 days/week for 12 months	86 400	Therapeutic stimulation
Stackhouse *et al.*, 2007[26]	50 Hz stimulation; pulse duration between 5 and 200 μs intensity 20 mA; 3 s ramp-up time; on:off time 15 : 45 s	3 days/week for 12 weeks (each muscle)	1 080	Percutaneous neuromuscular stimulation

(continued)

Table 2 Continued

Steinbok *et al.*, 1997[14]	35 Hz stimulation; pulse duration 300 ms; <10 mA intensity; on:off time 8 : 8 s with 2 s rise; 480–720 min	6 nights/week for 12 months	138 240–207 360	Therapeutic stimulation
van der Linden *et al.*, 2003[46]	Asymmetrical rectangular biphasic pulse; 5–15 s on:off cycle; rest period 5–15 s; duration 60 min. Varying frequency: 10 Hz–1st week; 30 Hz–1st session, 2nd week; 10 Hz–2nd session, 2nd week. Time between pulses: 75 ms–1st week, 100 ms–1st session and 75 ms–2nd session, 2nd week	6 days/week for 8 weeks	2 880	Neuromuscular stimulation
van der Linden *et al.*, 2008[21]	Amplitude range 20–70 mA; pulse duration 3–350 µs; frequency: 40 Hz (FS); duration whole day, except sports activity time	6 days/week for 8 weeks	Not specified	Functional stimulation

NMES, neuromuscular electrical stimulation; TES, therapeutic electrical stimulation; FS, functional stimulation.

separately two authors coded the studies and extracted data (SN and WH). Any coding disagreements were discussed by the three other authors (JC, SC and KH) until a consensus was reached.

Establishing outcome measures

The outcomes of each study were categorized according to the World Health Organization International Classification of Functioning, Disability, and Health (ICF-7).[54,55] Specifically, outcomes were classified in terms of impairment (e.g. range of motion) and activity limitations (e.g. gross motor function). To determine the effect of three common types of electrical stimulation on gait in cerebral palsy individuals, common outcome measures were selected and the results of each measure were standardized. Consistent with meta-analytic recommendations, we selected only one outcome measure per study per disablement category to avoid data biasing.[56] One exception is the study by Kerr *et al.* (2006) which used two separate comparisons and outcome measures.[22]

The primary outcome measures for the current meta-analyses were different for each classification category. For impairment, three outcome measures were reported: (a) range of motion (9 studies), (b) torque/moment (3 studies), and (c) strength/force (2 studies). For the activity limitations-based investigations, six dependent measures were recorded: (a) gross motor functions (6 studies), (b) gait parameters (i.e. symmetry, stride length or speed; 5 studies), (c) hopping on one foot (1 study), (d) videotaped 6-m walk (1 study), (e) Leg Ability Index[23] (1 study) and (f) Gillette gait index[57] (1 study). The specific outcome measures used in our meta-analysis as well as the respective experimental designs for each study were included in Tables 4 and 5.

The outcome data were submitted to random effects models from two types of experimental designs (a) between-subjects (i.e. electrical stimulation treatment groups versus no stimulation control groups) and (b) within-subjects (i.e. electrical stimulation groups who served as their own controls).[20,58,59] Studies that used the pretest–posttest within-subjects design permitted data coding on the same stimulated limbs. Moreover, retaining 14 within-subjects design studies increased our number of participants in the summary effect

Table 3 Quality assessments for each study included in the meta-analysis

Study	Experimental design	Random assignment	Single blind	Double blind	Drop-outs
Comeaux *et al.*, 1997[9]	Randomized cross-over design	1	0	0	0
Dali *et al.*, 2002[23]	Double-blind randomized trial	1	0	1	25
Durham *et al.*, 2004[49]	Quasi-experiment (non-randomized)	0	0	0	7
Hazlewood *et al.*, 1994[51]	Non-blind randomized trial	1	0	0	0
Ho *et al.*, 2006[38]	Randomized cross-over design	1	0	0	4
Jeronimo *et al.*, 2007[31]	Quasi-experiment (non-randomized)	0	0	0	5
Johnston *et al.*, 2004[50]	Quasi-experiment (non-randomized)	0	0	0	1
Katz *et al.*, 2008[24]	Case–control study	0	0	0	2
Kerr *et al.*, 2006[22]	Non-blind randomized trial	1	0	0	16
Khalili *et al.*, 2008[30]	Non-blind randomized trial	1	0	0	1
Maenpaa *et al.*, 2004[29]	Quasi-experiment (non-randomized)	0	0	0	0
Nunes *et al.*, 2008[27]	Single-blind randomized trial	1	1	0	0
Sommerfelt *et al.*, 2001[25]	Randomized cross-over design	1	1	0	4
Stackhouse *et al.*, 2007[26]	Non-blind randomized trial	1	0	0	2
Steinbok *et al.*, 1997[14]	Single-blind randomized trial	1	1	0	3
van der Linden *et al.*, 2003[46]	Single-blind randomized trial	1	1	0	0
van der Linden *et al.*, 2008[21]	Single-blind randomized trial	1	1	0	4

Table 4 Impairment: summary statistics for the 14 studies included in the impairment meta-analysis

Study	Primary outcome measure/experimental design: between [B] and within [W] subjects	Subjects in stimulation/ control groups	Weighted effect size	Confidence interval (95%)	
Comeaux *et al.*, 1997[9]	Ankle range of motion: Gastrocnemius; NMES – No NMES/[W]	14/14	0.677	0.096	1.258
Hazlewood *et al.*, 1994[51]	Active ankle dorsi-flexion with knee flexed; stimulation–control/[B]	10/10	1.054	0.118	1.989
Johnston *et al.*,[50]	Passive ankle dorsi-flexion; baseline – 12 months [W]	8/8	0.846	0.038	1.653
Katz *et al.*, 2008[24]	Active knee moment for extension: ES assisted; pre ES–post ES [W]	5/5	1.260	0.086	2.433
Kerr *et al.*, 2006[22]	Peak torque, most affected leg: post NMES; NMES–placebo/[B]	17/19	0.485	−0.179	1.485
Kerr *et al.*, 2006[22]	Peak torque, most affected leg: post TES; TES–placebo/[B]	17/19	0.285	−0.373	0.942
Khalili *et al.*, 2008[30]	Passive knee extension pre ES–post ES/[W]	10/10	0.758	0.055	1.462
Maenpaa *et al.*, 2004[29]	Active ankle dorsi-flexion with knee flexed; pre NMES–post NMES/[W]	17/17	0.988	0.489	1.486
Nunes *et al.*, 2008[27]	Active ankle range of motion: 14th session; pre NMES–post NMES/[W]	5/5	1.242	0.075	2.408
Sommerfelt *et al.*, 2001[25]	Ankle dorsi-flexion: sitting; TES – observation period/[W]	12/12	0.281	−0.296	0.858
Stackhouse *et al.*, 2007[26]	Normalized triceps surae force; stimulation–volitional/[B]	5/5	1.467	0.070	2.863
Steinbok *et al.*, 1997[14]	Hip abductors strength: TES – no TES/ [B]	20/21	0.350	−0.267	0.967
van der Linden *et al.*, 2003[46]	Maximum passive hip extension; stimulation–control/[B]	11/11	−0.143	−0.980	0.693
van der Linden *et al.*, 2008[21]	Peak dorsi-flexion in swing; stimulation on – stimulation off/[W]	7/7	0.469	−0.184	1.122

NMES, neuromuscular electrical stimulation; TES, therapeutic electrical stimulation; ES, general electrical stimulation.

Table 5 Activity: summary statistics for the 15 studies included in the activity meta-analysis

Study	Primary outcome measure/experimental design: between [B] and within [W] subjects	Subjects in electrical stimulation/ control groups	Weighted effect size	Confidence interval (95%)	
Dali *et al.*, 2002[23]	Leg ability index; pre TES–post TES/[W]	57/57	0.161	−0.100	0.422
Durham *et al.*, 2004[49]	Foot contact symmetry; pre FES–post FES/[W]	9/9	0.769	0.025	1.512
Hazlewood *et al.*, 1994[51]	Gait patterns; pre TES–post TES/[W]	10/10	4.129	0.730	7.528
Ho *et al.*, 2006[38]	Non-adjusted variables–stride length; FES–no FES/[W]	9/9	0.346	−0.327	1.018
Jeronimo *et al.*, 2007[31]	Step symmetry; pre ES–post ES/[W]	5/5	2.122	0.542	3.703
Johnston *et al.*, 2004[50]	Gross motor function: standing; baseline – 12 months/[W]	8/8	0.846	0.038	1.653
Kerr *et al.*, 2006[22]	Gross motor function: post NMES; NMES–placebo/[B]	17/19	0.536	−0.130	1.202
Kerr *et al.*, 2006[22]	Gross motor function: post TES; TES–placebo/[B]	17/19	0.103	−0.552	0.758
Maenpaa *et al.*, 2004[29]	Hopping on one foot; pre NMES–post NMES/[W]	23/23	0.711	0.254	1.169
Nunes *et al.*, 2008[27]	Gross motor function: 14th session; pre NMES–post NMES/[W]	5/5	1.260	0.086	2.433
Sommerfelt *et al.*, 2001[25]	Video evaluation by 3 physical therapists: TES–observation period/[W]	12/12	0.231	−0.342	0.805
Stackhouse *et al.*, 2007[26]	Walking speed; baseline–12 weeks/[W]	5/5	1.508	0.227	2.789
Steinbok *et al.*, 1997[14]	Gross motor function: TES–no TES/[B]	20/21	1.112	0.454	1.770
van der Linden *et al.*, 2003[46]	Gross motor function: section E; stimulation–control/[B]	11/11	0.082	−0.754	0.918
van der Linden *et al.*, 2008[21]	Gillette gait index; stimulation on–stimulation off/[W]	7/7	1.028	0.262	1.794

TES, therapeutic stimulation; FES, functional electrical stimulation; ES, general electrical stimulation; NMES, neuromuscular electrical stimulation.

meta-analyses of cerebral palsy gait and electrical stimulation treatments.

Data synthesis and analysis

Rosenthal *et al.* aptly contrasted the synthesis versus analysis functions inherent in a meta-analysis.[60] Synthesis functions include describing the relevant properties of the collection of studies including effect sizes as a whole. In contrast, analysis functions involve calculating weighted effect sizes and identifying moderator variables that may explain the standardized mean difference effect sizes in a collection of common studies.[20,60]

In line with conventional meta-analysis purists,[20,58] we computed the standardized mean differences for individual effect sizes of the 17 cerebral palsy gait and electrical stimulation studies. For each study, mean effect sizes were calculated and these values were compared in standardized mean differences calculations to produce overall effect sizes. The Comprehensive Meta-Analysis software (Biostat, version 2.2.027, Englewood, NJ, USA) was used to ensure consistency in examining the 17 cerebral palsy gait and electrical stimulation studies.[61] Conventional meta-analysts use standardized mean differences for comparing data/findings from different studies and perhaps, different outcome scales. Moreover, computing standardized mean differences is a robust and traditional meta-analysis technique for determining individual effect sizes incorporating the adjusted pooled variance.[20,58–60,62,63] Indeed, our effect sizes were weighted by reciprocal variances to derive the overall corrected mean effect size.[59]

Measuring the contribution of moderator variables on individual effect sizes is a third meta-analytic technique that we completed.[59,64] Given that a majority of the participants in these studies were categorized as either hemiplegia or diplegia,

we explored the possibility that individual effect sizes varied depending on a specific cerebral palsy condition.

Measuring heterogeneity

Meta-analysts typically compute heterogeneity tests that contrast the inherent variability of individual studies that includes variability in all phases of an experiment (e.g. participants, treatments, outcome measures or experimental design). Recently, Higgins *et al.* advocated a technique called I^2 for measuring variability by examining the spread in the studies, determining the consistency of evidence beyond a statistical chance occurrence and representing heterogeneity as a percentage.[65] This heterogeneity test involves calculating the ratio of true heterogeneity to total observed variance.[61]

Initially, there appeared to be a considerable amount of variance in the studies. One of the reasons for such variability may be the subtle differences in the basic techniques involved in functional and neuromuscular stimulation. Specifically, functional stimulation is applied to the muscle or nerve during the time the muscle would normally be active. For instance, Holt *et al.* administered functional stimulation to the gastroc-soleus muscles during the mid to late stance phase through push-off while walking.[66] Conversely, neuromuscular stimulation has no such restriction and this stimulation is provided to produce a muscular contraction. In addition, the goals of these two stimulation protocols are different. Functional electrical stimulation's goal is to improve muscle functions during the time at which the muscle would be normally active, whereas the goal of neuromuscular electrical stimulation is muscular strengthening. Thus, these two types of electrical stimulation are homogeneous in name only. Although comparisons across these two types of stimulation may not appear at first glance to be homogeneous, our conservative approach in testing heterogeneity with the I^2 statistic is a robust technique for quantifying this important relationship in cerebral palsy gait.[65]

Publication bias and fail-safe *N* analysis

Publication bias arises when the probability of publishing a study increases as the effect size of the reported findings increase. To evaluate publication bias we plotted the effect size of individual studies against the standard error associated with each study.[58,59,61,64] Ideally, such a funnel plot demonstrates symmetry across studies of different size and precision with smaller and larger studies scattered uniformly at the base and apex of the funnel.

A second effective meta-analytic technique for evaluating publication bias is the classic fail-safe *N* analysis.[20] This technique computes the number of studies with non-significant findings required to nullify the overall effect calculated in the current analysis. Larger fail-safe *N*-values increase confidence in the overall effects and assist in validating the stability of findings.

Results

Based on the International Classification for functioning system (i.e. impairment and activity limitations) specific studies and their respective outcome measures were submitted to separate random effects model meta-analyses. Of the 17 total studies on children with cerebral palsy with gait problems and electrical stimulation used as an intervention, 14 studies focused on impairment and 15 focused on activity. The findings shown in Tables 4 and 5 represent the meta-analyses on the two functional classifications.

Impairment meta-analysis

Systematic analysis of the 14 impairment studies indicated a significant standardized mean effect equal to 0.616 ($SE = 0.10$; $P < 0.0001$) with a 95% confidence interval of 0.420 to 0.812. These values indicate that the summary effect was significant and represented a moderate effect size.[20,58,67] These studies that investigated impairment deficits tested 302 total subjects with 158 subjects in electrical stimulation groups and 144 in no stimulation groups (66 between-subjects and 78 within-subjects). Individual effect sizes for the studies ranged from –0.0143 to 1.467. For each study, Table 4 shows the individual weighted effect sizes with lower and upper limit confidence intervals.

Visually representing the amount of variation in the studies, as well as an estimate of the overall effect size for all studies is referred to as a

forest plot. Figure 1 shows the forest plot of effect sizes for each of the 14 impairment studies as a tick mark in the centre of the line and the 95% confidence interval at the distal of ends of each line. Impairment studies in the forest plot were grouped by type of electrical stimulation treatment. From the top down, studies were displayed as single lines of various lengths (confidence intervals). The diamond shapes represent summary effect sizes and confidence intervals of the studies (listed above) for a specific type of stimulation. The diamond at the bottom of the figure refers to the pooled point estimate of all studies in the meta-analysis (0.5890). The current analysis revealed a robust forest plot as well as a medium effect size for the impairment studies.

Measuring heterogeneity

Variability calculations on the 14 impairment studies revealed an $I^2 = 4.89$. This small value indicates a low amount of inconsistency in the studies.[56,65] The proportion of observed dispersion in the impairment studies that is real is relatively small as I^2 approaches zero, consequently, random error explains most of the dispersion.[61] Further, according to formulas provided by Borenstein *et al.*, the confidence intervals for this small amount of inconsistency were 0.0–57.32.[61]

Publication bias and fail-safe N *analysis*

Publication bias in the impairment studies was determined by two funnel plots (Figures 2 and 3). The scatterplots show treatment effect size on the *x*-axis and standard error (study size) on the *y*-axis. Most importantly, the funnel plots indicate a small amount of publication bias as the studies displayed a relatively symmetrical distribution around the individual effect sizes, as well as a small effect of two imputed comparisons required to balance the funnel (Figure 3).

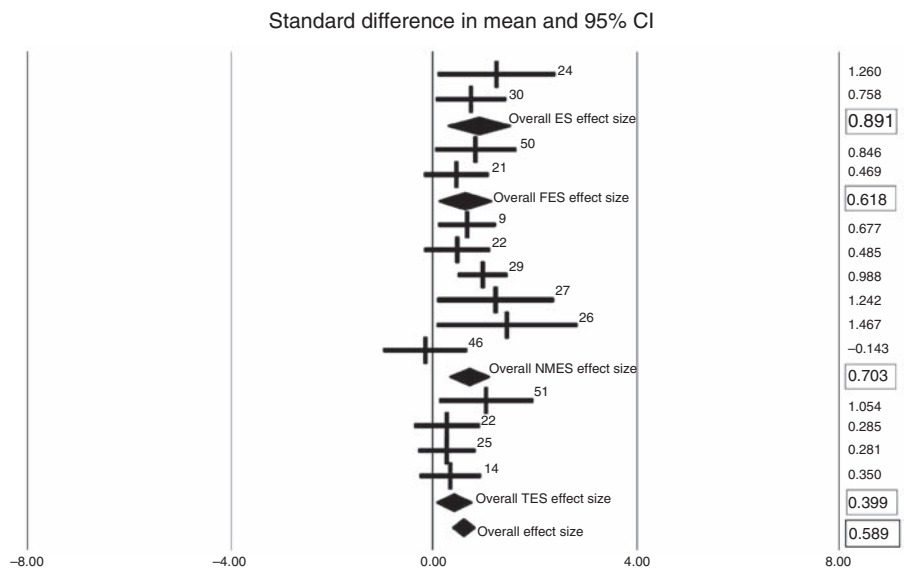

Figure 1 Forest plot showing individual effect sizes for the 14 cerebral palsy gait and electrical stimulation studies based on the impairment meta-analysis. Studies were grouped by type of electrical stimulation intervention. The stimulation provided in two studies did not clearly fall into any of the three types, thus, a separate general electrical stimulation heading was created. The five diamond shapes represent overall (summary) effect size calculations. The super script numbers next to each line indicate the reference number for each study. The far right column lists effect sizes found for the impairment meta-analysis. ES, general electrical stimulation; FES, functional electrical stimulation; NMES, neuromuscular electrical stimulation; TES, therapeutic electrical stimulation.

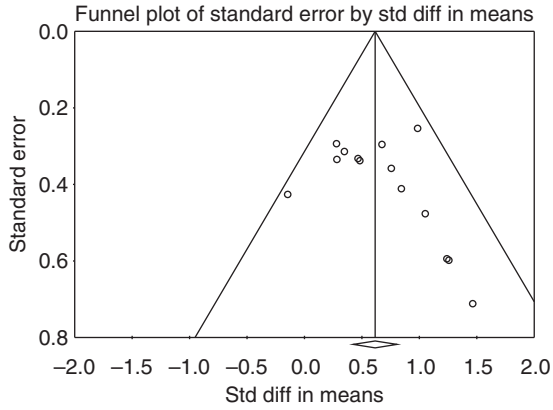

Figure 2 Impairment meta-analysis funnel plot evaluating publication bias. Each circle denotes an individual study with a specific effect size (*x*-axis) and standard error (*y*-axis).

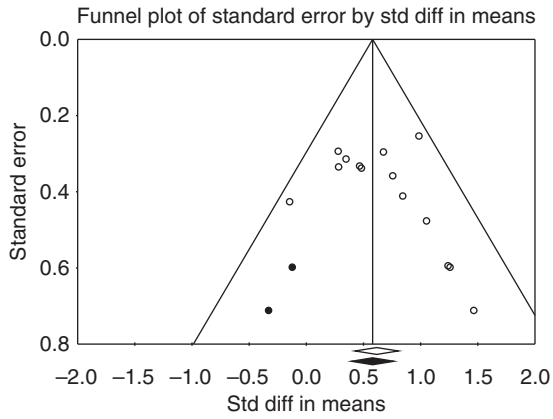

Figure 3 Impairment meta-analysis funnel plot with two imputed studies (black circles). Mathematically calculating and inserting imputed studies serves as a best estimate of a symmetrical funnel, an unbiased effect across all studies.

Further, the fail-safe *N* analysis determined that 139 null effect findings were necessary to lower the summary effect size to an insignificant level. Requiring such a high number of null findings reveals stability in the summary effect size. The relatively high standardized mean effect size clearly shows that the three types of electrical stimulation do change the impairments associated with cerebral palsy walking.

Moderator variable analysis

Examining the type of electrical stimulation as potential moderating variables affords additional insight into the summary effect. For the moderator analysis, we grouped the impairment studies by type of electrical stimulation: (a) functional (2), (b) neuromuscular (6), and (c) therapeutic (4). As shown in Table 4, two studies did not provide specific details on the type of electrical stimulation provided; consequently, we labelled them general electrical stimulation.[24,30] Overall, the subgroup analyses revealed a significant moderate effect size equal to 0.59 (SE = 0.107; $P < .0001$). Moreover, each of the types of stimulation made significant contributions as moderator variables: (a) functional = 0.618; $P < 0.01$; $Z = 2.38$; $I^2 = 47.7$; (b) neuromuscular = 0.703; $P < 0.0001$; $Z = 4.85$; $I^2 = 18.2$; and (c) therapeutic = 0.40; $P < 0.02$; $Z = 2.357$; $I^2 = 53.5$; and (d) general = 0.89; $P < 0.004$; $Z = 2.89$; $I^2 = 47.29$.

A second moderator variable analysis involved the type of cerebral palsy. However, given the mixed cerebral palsy types (diplegia and hemiplegia) found throughout the studies and treatment conditions, the effect of these potential moderator variables was not discernible.

Activity limitations meta-analysis

A separate meta-analysis focused on the 15 cerebral palsy gait and electrical stimulation studies reporting activity limitations. The random effects model identified a significant effect equal to 0.635 (SE = 0.136; $P < .0001$) with a 95% confidence interval of 0.369 to 0.901.[20,58,67] The activity level deficits studies tested 416 total subjects with 215 subjects in electrical stimulation groups and 201 in no stimulation groups (i.e. 51 between-subjects and 150 within-subjects). Individual effect sizes ranged from 0.082 to 4.130. Table 5 displays the weighted effect sizes with respective lower and upper limit confidence intervals. In addition, Figure 4 displays a forest plot of the individual effect sizes for the activity limitations analysis.

In summary, both the confidence interval data and the forest plot indicate that children with cerebral palsy who experienced one of three electrical stimulation protocols showed more gait capabilities than before the treatment intervention. The activity disablement category does not appear as severe post treatment.

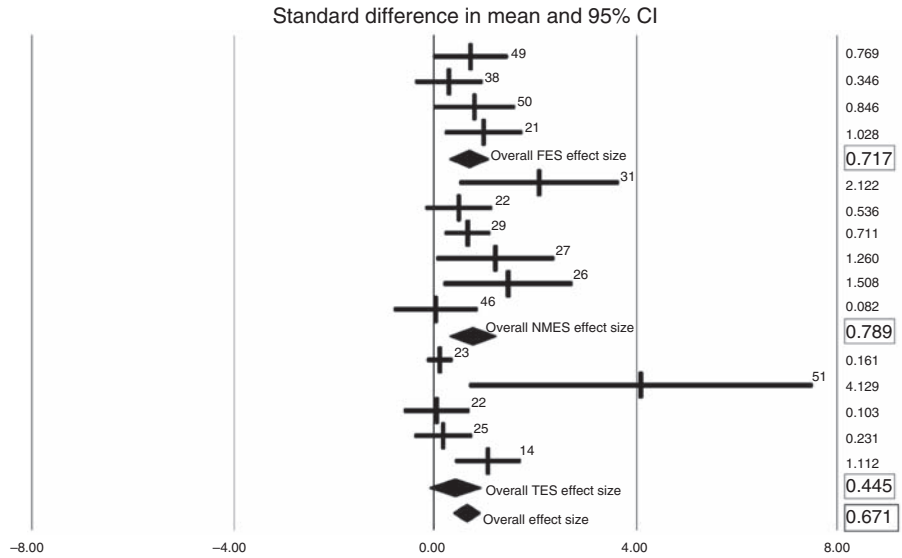

Figure 4 Forest plot showing individual effect sizes for the 15 cerebral palsy gait and electrical stimulation studies based on the activity limitations meta-analysis. Studies were grouped into one of three types of electrical stimulation. The four diamond shapes represent overall (summary) effect size calculations. The superscript numbers next to each line indicate the reference number for each study. The far right column lists effect sizes found for the activity limitations meta-analysis.

Measuring heterogeneity

Variability calculations on the 15 activity studies revealed an $I^2 = 52.30$, a moderate amount of inconsistency with confidence intervals: 16.00–72.93. Such a value warrants additional moderator variable or subgroup analyses.[56,63,65,68] Borenstein *et al*. stated that the proportion of variance that is true, rather than spurious, is found in the descriptive statistic I^2 as values move away from zero.[61]

Publication bias and fail-safe N *analysis*

The funnel plots shown in Figures 5 and 6 reveal relatively little publication bias in the 15 studies of gait and electrical stimulation. Similar to the impairment studies, the activity investigations show nearly a symmetrical distribution around the individual effect sizes. Moreover, the six imputed values, black circles on the left side of the funnel plot shown in Figure 6, present an ideal attempt at symmetry.

In addition, the fail-safe N analysis calculations derived the number of null effect results ($N = 183$) necessary for lowering the effect size to an insignificant level. Together, the funnel plot and fail-safe analysis support the conclusion that the high-end standardized mean effect size indicates that the three types of electrical stimulation minimized the activity limitations associated with gait.

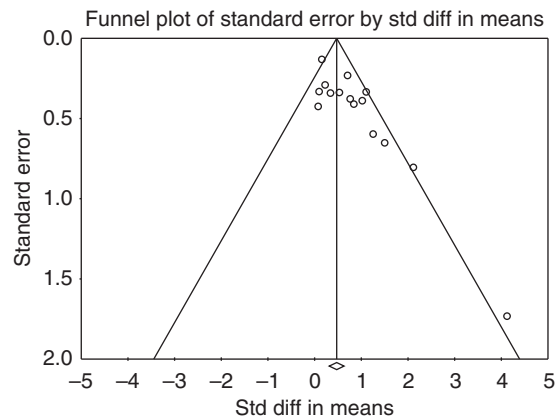

Figure 5 Activity limitations meta-analysis funnel plot evaluating publication bias. Each circle denotes an individual study with a specific effect size (*x*-axis) and standard error (*y*-axis).

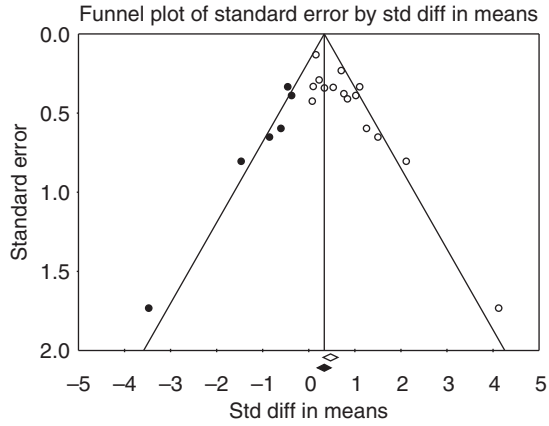

Figure 6 Activity limitations meta-analysis funnel plot with six imputed studies (black circles). Mathematically calculating and inserting imputed studies serves as a best estimate of a symmetrical funnel, an unbiased effect across all studies.

Moderator variable analysis

Conducting additional subgroup analyses on the three types of electrical stimulation as possible moderating variables on the activity limitations studies provided comprehensive findings. Results identified an overall effect size equal to 0.671 (SE = 0.125; $P < .0001$). Further meta-analyses revealed significant contributions from each associated electrical stimulation type: (a) functional = 0.717; $P < 0.0002$; $Z = 3.79$; $I^2 = 1.39$; (b) neuromuscular = 0.789; $P < 0.0005$; $Z = 3.52$; $I^2 = 36.06$; and (c) therapeutic = 0.445 $P < 0.02$; $Z = 2.58$; $I^2 = 67.13$.

At the top of Figure 4, diamonds representing functional and neuromuscular highlight the contribution of each type of stimulation to minimizing the activity disablement classification in the studies. On the other hand and contrary to Pape's comprehensive review, therapeutic stimulation as a moderator variable did not reveal any significant contribution to the activity limitation effect.[42]

Discussion

The current findings tentatively support treating walking impairments and activity limitations of children with cerebral palsy with electrical stimulation. Separate meta-analyses on each functional classification indicated improved walking capabilities post treatment. The two reliable and medium effect sizes found for impairment and activity limitations indicate medium sized summary effects across over 400 children with walking problems for 29 independent stimulation comparisons (i.e. 14 impairment and 15 activity limitations studies). The random effects models findings on three primary electrical stimulation treatments are encouraging in that this evidence is consistent with a comprehensive qualitative review by Kerr *et al.* in that electrical stimulation protocols represent a viable treatment protocol for children with cerebral palsy and walking problems.[40]

Furthermore, separate subgroup analyses on the impairment and activity limitation studies indicated reliable contributions by each type of electrical stimulation. One exception was therapeutic stimulation for activity limitations. Figures 1 and 4 highlight the individual effect sizes for each stimulation type. Even though the moderator variable analyses revealed support for differential contributions by functional, neuromuscular and therapeutic electrical stimulation, the small number studies warrants caution.

Reservations about cerebral palsy, gait and electrical stimulation

The present systematic review highlights the many roadblocks to being able to recommend electrical stimulation as an efficacious intervention for individuals with cerebral palsy. Unfortunately, we are unable to comment on the accrued benefits to daily walking challenges outside these laboratory-testing experiments. No quantitative, functional immediate or longitudinal effects beyond the testing situations were reported in these studies. Thus, long-term effects of various types of electrical stimulation on gait challenges in children with cerebral palsy would advance our understanding. We urge clinicians and researchers to pursue this important line of investigation.

Additional complications in determining electrical stimulation effects on the gait of children with cerebral palsy include: (a) age, (b) location on the body for stimulation (e.g. dorsi-flexors vs. plantar-flexors of the ankle), (c) stimulus parameters (i.e. intensity, duration, frequency and number of sessions), and physiological responses. Granted, the

present systematic review and meta-analysis findings supplement the current practice of evidence-based medicine in selecting treatment interventions. However, a better understanding of these effects will allow for more controlled studies as well as help clinicians make decisions about parameter values for individual children.

An implication of this systematic review and meta-analysis is the need for an increased understanding of the cerebral palsy pathology of causes and symptoms. The literature and conflicting evidence clearly indicate a compelling prerequisite in establishing a sound theoretical base that will provide hypothesis-driven answers for selecting appropriate interventions. Ideally, effective cerebral palsy interventions will evolve from theoretically unassailable research that produces a critical mass of empirical evidence on treatments affecting gait.

Meta-analytic techniques

Given the absence of systematic research that determined the amount of electrical stimulation necessary to achieve immediate as well as long-lasting effects for children, we conducted the present meta-analysis. Standardized mean difference effect sizes were calculated because conventionally, systematic meta-analytic techniques readily accommodate outcome data from a broad group of studies including heterogeneous studies.[61] Moreover, closely following the guidelines for systematic reviews and meta-analyses outlined by the Cochrane Libraries accommodates data pooling from different studies that varied on treatment interventions and overall goals.[56,61] Specifically, our random effects model meta-analyses on the three types of stimulation studies accommodated data arising from the differing experiments. Indeed, the fail-safe analysis revealed that a high number of null findings are necessary to eliminate the identified functional classification of impairment and activity limitations post treatment. Furthermore, using multiple meta-analysis techniques, including composite scores for a majority of the studies as well as funnel and forest plots ensured rigorous overall effect sizes while examining the effects of potentially critical moderating variables.[58,61]

Conclusion

In conclusion, this is the first meta-analysis conducted on the effectiveness of electrical stimulation for walking problems found in children with cerebral palsy. Our systematic meta-analyses revealed medium summary effect sizes indicating support for using electrical stimulation as an intervention in children with cerebral palsy and associated gait problems seen as walking impairments and activity limitations. Given the complications of cerebral palsy and the minimal number of double-blinded randomized control trials in the literature, we cautiously advocate that electrical stimulation be used to minimize impairment and activity limitations in gait. These findings corroborate earlier qualitative reviews, as well as highlight shortcomings in the literature.[40,51] Furthermore, advances in solving walking problems in children with cerebral palsy will come from a large-scale set of related experiments based on a sound theoretical and experimental understanding of neuromuscular functions.

Clinical messages

- Robust meta-analyses indicated that electrical stimulation produced medium effect sizes on gait outcomes of children with cerebral palsy.
- Moderator variables analyses revealed that both functional and neuromuscular electrical stimulation treatments helped minimize impairment and activity limitations in walking.

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