What is the Effect of Motor Level Peripheral Electrical Stimulation on Corticospinal Excitability and Functional Outcome Measures in Both Healthy Participants and those with Neurological Disorders? A Systematic Review and Meta-Analysis

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Abstract

Introduction: To explore the effect of Motor Level peripheral Stimulation (MLS) on Corticospinal Excitability (CSE) in healthy participants and those with neurological disorders, and to establish stimulation parameters best suited to this purpose. **Methods and Materials**: A comprehensive search strategy was developed for identification of papers answering the review question. The studies identified were used to do meta-analyses. **Results:** Following motor-level stimulation, there was a significant change in CSE from baseline: 57.66% (95% CI). Subgroup analysis showed that there was a significant change in the 100Hz subgroup: 68.31% (95% CI) and the 20-50Hz subgroup: 80.14% (95% CI), but not in the <10Hz subgroup: 9.97% (95% CI). In addition, CSE changes was greater where intervention time = 30mins: 83.19% (95% CI), then where intervention time >30mins: 53.14% (95% CI). CSE showed no significant changes following 'no stimulation": 69.61% (95% CI). **Conclusions:** The findings indicate that MLS leads to increases in CSE; however, magnitude of change depends on the stimulation frequency and the area stimulated. It also appears that stimulation durations of longer than 30mins do not result in greater changes. **Significance:** The present review article hopes to catalyze further research into the determination of appropriate MLS treatment parameters for specific muscle groups.

Key words: Motor level stimulation, corticospinal excitability, functional electrical stimulation, associative stimulation, transcranial magnetic stimulation, motor evoked potentials

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Introduction

The motor cortex is highly plastic, and is subject to reorganization. Primary motor cortex (M1) plasticity is normally modulated by voluntary cortical activation paired with afferent feedback [1]. Function-enabling plasticity is commonly observed in athletes and musicians preforming repeated task-based practice [2]. Conversely, chronic disuse, such as is found in long periods of recumbence, neurological dysfunction, or amputation drives function-disabling plasticity [3]. Manipulation of processes underlying these adaptations is an area of significant research aimed at actuating optimal motor relearning in neurological rehabilitation.

Modulation of Corticospinal (CS) output has been shown to be correlated with early stages of motor learning. Increases in Corticospinal Excitability (CSE) are associated with improved motor function after stroke[4], spinal cord injury[5], and other Central Nervous System (CNS) conditions[6]. Repeated activation of these pathways leads to long term cortical structural changes correlated with motor recovery [7].

Motor Level Stimulation (MLS) is widely used to facilitate motor relearning in situations where task-based training is difficult or not possible. The effects of MLS are routinely studied using functional outcome measures, and clinical benefit has been demonstrated in numerous high quality randomised trials. In patients following stroke, Faghri *et al.* and Powell *et al.* demonstrated an increase in the range of shoulder movement and arm function, and wrist extensor strength, respectively[4, 8]. Mulcahey *et al.* observed an improvement in the Activities of Daily Living Measures in patients with spinal cord injury

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following the application of hand stimulation[9]. There are numerous other papers demonstrating functional improvement, but while these measures are clinically useful, they are not sufficiently sensitive for detection of subtle changes in single session interventions and do not reveal the mechanisms behind improvements in motor function. Physiological outcome measures can expose what structures and systems are modified during therapy, and uncover optimal parameters for the development of evidence-based treatment protocols.

Early animal and human studies supported the hypothesis that MLS induces motor re-education through its actions on a local level via increases in capillary density and transformation of fibre type. Rochester et al. stimulated Tibialis Anterior (TA) for four weeks, at 10Hz, with an intensity twice the motor threshold [10]. Post-stimulation muscle biopsies revealed an improvement in oxidative capacity. Brown et al. showed an increase in capillary density in rabbits following 28 days of electrical stimulation at 5-40Hz, above motor threshold, for 8h/day [11]. Pette and Heilmann showed a transformation of fibre type from fast to slow twitch following continual MLS in rats [12]. More recently, Rushton suggested that MLS induces plasticity in peripheral neurons [13]. This contention is supported by Randic *et al.* who demonstrated Long Term Potentiation (LTP) in the spinal dorsal horn following brief, high-frequency stimulation in a rat mode l[14], and by Pockett and Figurov who observed similar changes in the ventral horn [15].

Transcranial Magnetic Stimulation (TMS) induced Motor evoked Potentials (MEPs) have allowed the quantification of CS responses in a painless and non-invasive manner. Corollary to this, recent research has focused on identifying cortical changes that occur in response to MLS in humans.

Induction of movement using MLS simulates voluntary movement and simultaneously provides both tactile and proprioceptive afferent input secondary to imposed movement. Cortical changes resulting from stimulation may be a product of sensory-motor integration: the synergistic relationship between the sensory and motor systems [16]. Increases in excitability time strengthen CS circuits may over, and so, while the effects of a single session of MLS may be transient, repeated administration may lead to long-term improvement in motor function [7].

It has been suggested that synchronous firing to two different, yet functionally associated muscles may result in greater increases in CSE [17], which is termed Associative Stimulation (AS).

Functional Electrical Stimulation (FES) is a type of MLS designed to replicate or augment functional tasks. Liberson *et al.* were the first to apply electrical stimulation via the Common Peroneal Nerve (CPN) during the swing phase of gait and observed immediate improvement in walking performance [18]. They also noted long term improvement post intervention. This carry over effect has been reproduced by Stein et al. in a multicenter study [19], and by Ladouceur and Barbeau in a longitudinal study [20]. These clinical improvements have been observed in stroke [21] and spinal cord injury patients[22]. The mechanisms behind long-term improvements are unclear; however, there have been several studies that have examined the effects of FES on M1 excitability.

While peripheral stimulation may show promise in the management of neurologically impaired patients, optimal stimulation parameters remain a point of contention. The focus of the present review was to summarise findings related to the effect of MLS on changes in MEPs, to identify studies where both neurophysiological and functional outcome measures have been used and to determine whether a correlation has been demonstrated, and to conduct a subgroup meta-analysis to determine which parameters, if any, result in superior changes in cortical measures. In contrast to many clinical trials, neurophysiological studies tend to use baseline scores for statistical analysis. A secondary focus of the current review was to identify papers that included a 'no stimulation' experimental group and to determine whether MEP amplitudes tend to change significantly from baseline as a result of either time, or repeated assessment using TMS, and therefore determine whether repeated measures studies are appropriate trial types for this research.

Objectives

Primary aim:

To explore the effect of MLS on CSE as quantified by TMS induced MEPs in healthy participants and those with neurological disorders.

Secondary aims:

1. To explore whether changes in CSE are accompanied by changes in functional outcome measures in healthy participants and those with neurological disorders
2. To explore whether there is a difference from baseline MEP amplitude following no/sham treatment protocols, and consequently determine whether observed changes are a product of the intervention in question
3. To explore the effect of various stimulation frequencies, in different afferent pathways, on CSE modulation
4. To explore the effect of intervention duration on induction of CS changes

Methods

Search strategy

MEDLINE (1946 to present), Scopus SciVerse, PubMed, Cochrane Central Register of Controlled Trials, AMED (1985 to present), and EMBASE were searched. No date limit was applied to the search. Also, literature was scanned for the reference lists of the key articles. A search of grey literature was performed using the following sources: The Agency for Healthcare Research and Quality, Open Grey, The Australian New Zealand Clinical Trials Registry, and Current Controlled Trials metaRegister of Controlled Trials.

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Table 1. *Inclusion Criteria*

	Included:	***Excluded:***
Participants	Healthy Individuals; Individuals with neurological disorders.	Animal Studies; Unconscious Individuals.
Interventions	MLS; FES; AS.	Sensory level peripheral stimulation; Noxious level peripheral stimulation; Paired Associative Stimulation; Any central stimulation including but not limited to tDCS and TMS.
Trial design	Randomized controlled trial including: Cross over trials; Cluster randomised trials. Quasi-experimental studies including: Non-randomised controlled trials; Pre-test post-test study designs; Interrupted time series designs.	Literature Reviews; Case Reports; Case Series.
Outcomes	Peak-peak amplitude of MEP as a measure of CSE; Any functional measure.	Any study that does not report a measure of amplitude changes in MEP; MEP as measured by the triple stimulation technique.
Publications	Peer reviewed journals; Books; Conference abstracts; Theses; Any year of publication.	Publications in any language other than English, unless a translation is provided.

Table 2. *Overview of included papers*

Reference	Quality Score /10	Sample Size	Participant Profile	Stimulation Type
Barsi e*t al.* (2008a)	4	25	Healthy	FES
Chang *et al.* (2011)	4	17	Healthy and Spinal cord lesions	MLS
Charlton *et al.* (2003)	5	12	Healthy	MLS and AS
Chen *et al.* (2015)	5	27	Healthy and spino-cerebellar Ataxia	MLS
Chipchase *et al.* (2011a)	5	10	Healthy	MLS
Everaert *et al.* (2010b)	5	36	Progressive and non-progressive CNS disorders	FES
Hindle *et al.* (2014)	5	40	Healthy	MLS
Khaslavskaia and Sinkjaer (2005)	5	10	Healthy	MLS
Khaslavskaia *et al.* (2002a)	5	12	Healthy	MLS
Kido Thompson and Stein (2004)	4	10	Healthy	FES
Knash *et al.* (2003)	5	14	Healthy	MLS
Lagerquist *et al.* (2012)	5	10	Healthy	MLS
Liao *et al.* (2008)	5	6	Incontinent	MLS
Mang *et al.* (2011)	4	14	Healthy	MLS
Mang *et al.* (2012)	5	9	Healthy	MLS
Mang et al. (2010)	5	8	Healthy	MLS
McDonnell and Ridding (2006)	4	27	Healthy	AS
McKay *et al.* (2002)	4	10	Healthy	AS
Pitcher and Miles (2002)	5	12	Healthy	MLS
Pyndt and Ridding (2004)	5	12	Healthy	AS
Ridding *et al.* (2001)	4	14	Healthy	AS
Schabrun *et al.* (2012)	4	13	Healthy	MLS
Thompson *et al.* (2006)	4	14	Healthy	FES
Thompson *et al.* (2011)	4	10	Incomplete spinal cord lesions	MLS
Uy and Ridding (2003)	4	10	Healthy	MLS

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Table 3. *No/Sham Stimulation Control-% change MEP from baseline*

Reference	No Stim or Sham	Participant #	Muscle Tested	% change from baseline MEP
Golaszewski *et al.* (2009)	Sham	28	FDI	16
Golaszewski *et al.* (2012)	Sham	12	FDI	-12
.Kaelin-Lang *et al.* (2002)	No Stim	11	ADM	3
Khaslavskaia *et al.* (2002a)	Sham	3	FDI	-2
McKay *et al.* (2002)	Sham	7	FDI	16
Ridding *et al.* (2001)	Sham	6	FDI	-10
Uy and Ridding (2003)	No Stim	10	FDI	-10

Table 4. *Motor Level Stimulation-% change MEP from baseline*

First Author/Date	Participant Profile	Nerve Stimulated	Frequency	Pulse Duration (ms)	Time (min)	Muscle	% change from baseline MEP	
							t=0-15min	t=15-30min
Chang (2011)	Healthy	Median	25Hz	-	30	FCR	154±29%	
	SCI	Median	25Hz	-	30	FCR	-4±13%	11±13%
Charlton (2003)	Healthy	Ulnar	10HZ	1	120	FDI	13±15%	6±11%
Chen (2015)	SCA	Median	25Hz	0.8	30	FCR	56 ±27%	55±26%
Chen (2015)	Healthy	Median	25Hz	0.8	30	FCR	55±10%	50±10%
Chipchase (2011)	Healthy	Musculo cutaneous	10Hz	0.1	30	Biceps Brachii	-10±8%	
	Healthy	Musculo cutaneous	30Hz	0.1	30	Biceps Brachii	123±30	
Golazewski (2012)	Healthy	Whole hand	2Hz	0.3	30	FDI	13±6%	
Hindle (2014)	Healthy	Common peroneal	100Hz	0.05-1	30	TA	44±20%	
Khaslavskaia (2002)	Healthy	Common Peroneal	200Hz	1	30	TA	104±26%	70±26%
Khaslavskaia (2005)	Healthy	Common Peroneal	30Hz	1	30	TA	38±16%	23%
Knash (2003)	Healthy	Common Peroneal	25Hz	1	30	TA	50±14%	28±18
Lagerquist (2012)	Healthy	Tibial	100HZ	1	40	SOL	18±26%	
Liao (2008)	Incontinent	S2-S4	-	-	7 days	FHB	8±11%	
Mang (2010)	Healthy	Common Peroneal	10	1	40	TA	27±10%	
	Healthy	Common Peroneal	50	1	40	TA	54±28%	
	Healthy	Common Peroneal	100	1	40	TA	101±28%	
Mang (2011)	Healthy	Common Peroneal	100Hz	1	40	TA	88±22%	
Mang (2012)	Healthy	Ulnar	100Hz	1	40	FDI	70±29	
Pitcher (2002)	Healthy	Ulnar	20Hz	0.1	Till fatigue	FDI	145±56	-33±11%
Schabrun (2012)	Healthy	Median	30Hz	0.1	30	APB	109±21%	
Thompson (2011)	Incomplete spinal cord lesions	Common Peroneal	25Hz	0.5	30	TA	26±8%	21±7%
Uy (2003)	Healthy	Ulnar	10Hz	1	30	FDI	-4%	-14%

Table 5. *Functional Electrical Stimulation*

Reference	Participant Profile	Nerve	Time	Muscle Tested	% change from baseline MEP		
					t=0-15min	t=15-30min	t=30+min
Everaert *et al.* (2010b)	Progressive	CPN	3 Months	TA	18±7%		
	Non-progressive	CPN	3 Months	TA	46±17%		
Thompson *et al.* (2011)	Healthy	CPN	30min	TA	31±11%	42±10%	33±11%
Barsi *et al.* (2008a)	Healthy	FDC+ EDC	20min	FDP	24±14%		
Kido Thompson and Stein (2004)	Healthy	CPN	30min	TA	27±8%	39±11%	

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Table 6. Associative Stimulation-% change MEP from baseline

Reference	Participant Profile	Frequency (Hz)	Time (min)	Muscle Tested	% change from baseline MEP		
					t=0-15min	t=15-30min	t=30+min
McDonnell and Ridding (2006)	Health	10	60	FDI	59±29%		
Pyndt and Ridding (2004)	Healthy	10	60	FDI	107±49%	109±50%	
Ridding *et al.* (2001)	Healthy	10	60	FDI	98 ± 45%	57%	
Charlton *et al.* (2003)	Healthy	10	120	FDI	13±10%	6±10%	-3±10%
McKay et al. (2002)	Healthy	10	120	FDI	53±12		

Table 7. Functional Outcome Measures

Reference	Date	% change from baseline MEP	Functional Outcome measure A	% change from baseline	Functional Outcome measure B	% change from baseline	Functional Outcome measure C	% change from baseline
Everaert *et al.* (2010b) (Progressive)	2010	18%	MVC (mV)	49%	Walking Speed (m/s)	24%		
Everaert *et al.* (2010b) (Non-progressive)	2010	46%	MVC (mV)	26%	Walking Speed (m/s)	7%		
Lagerquist *et al.* (2012)	2012	18%	MVC (Nm)	1%				
Liao *et al.* (2008)	2008	28%	Daytime frequency	-56%	Nocturia frequency	-62%	Pads/Day	-60%
McDonnell and Ridding (2006)	2006	59%	GPT completion time	-16%				

Inclusion and Exclusion Criteria

Table 1. Summarizes the inclusion and exclusion criteria in this study.

Quality Assessment

The PEDro scale was used to score studies on their quality and bias[23]. The scale contains 11 items. Items were scored 'yes' or 'no' depending on application of decision rules specified. Where a paper satisfied the item's decision rule, it received one point. The first item is not scored, therefore each study received a quality score of 0–10. Since baseline was used as control, papers received an automatic 'yes' for 'similarity at baseline' and 'treatment or control as allocated', and received a 'yes' for 'between group analysis' if they reported point measures and measures of variability.

Data Extraction

Data extracted for the review included: author, date, trial type, total number of participants, and number of participants in each group, participant profile, stimulation type, additional outcome measures, available point measures, and measures of variability for relevant outcome measures. Where results were displayed graphically, 'plot digitizer' was used to extract data. All the intervention results were transformed into 'percentage change from baseline'.

Missing data

Where the SE of change scores was not directly extractable, a conservative estimate was obtained using p values where available, or a best estimate was derived using the mean of standard errors scores in similar papers.

Meta-analysis

Using the generic inverse variance method, Meta-analysis was performed on percentage change in MEP from baseline using REVMAN for the following comparisons: MLS in healthy participants (frequency subgroups [10Hz, 20-50Hz, 100Hz] were chosen to create an even distribution of trials in each group), MLS in healthy participants (intervention time subgroups were chosen as equal number of trials used 30 min stimulation and >30min stimulation), MLS in Neurologically impaired participants, FES, AS, No Stimulation repeated measure, MLS at 20-50Hz (upper limb compared to lower limb, MLS at the CPN (100Hz compared to 20-50Hz).

Results

Results of the search

See Figure 1 for a graphical representation of the search process. One review article on a similar topic was identified[24].

Included Studies

See Table 2 for the details of included studies.

Quality Assessment

Most included papers used a similar design and as such there was a great degree of homogeneity in quality scores. The greatest source of bias was blinding and randomisation. Only one paper used random allocation[25] and none of the papers had used blinding. All the papers measured all key outcome measures and

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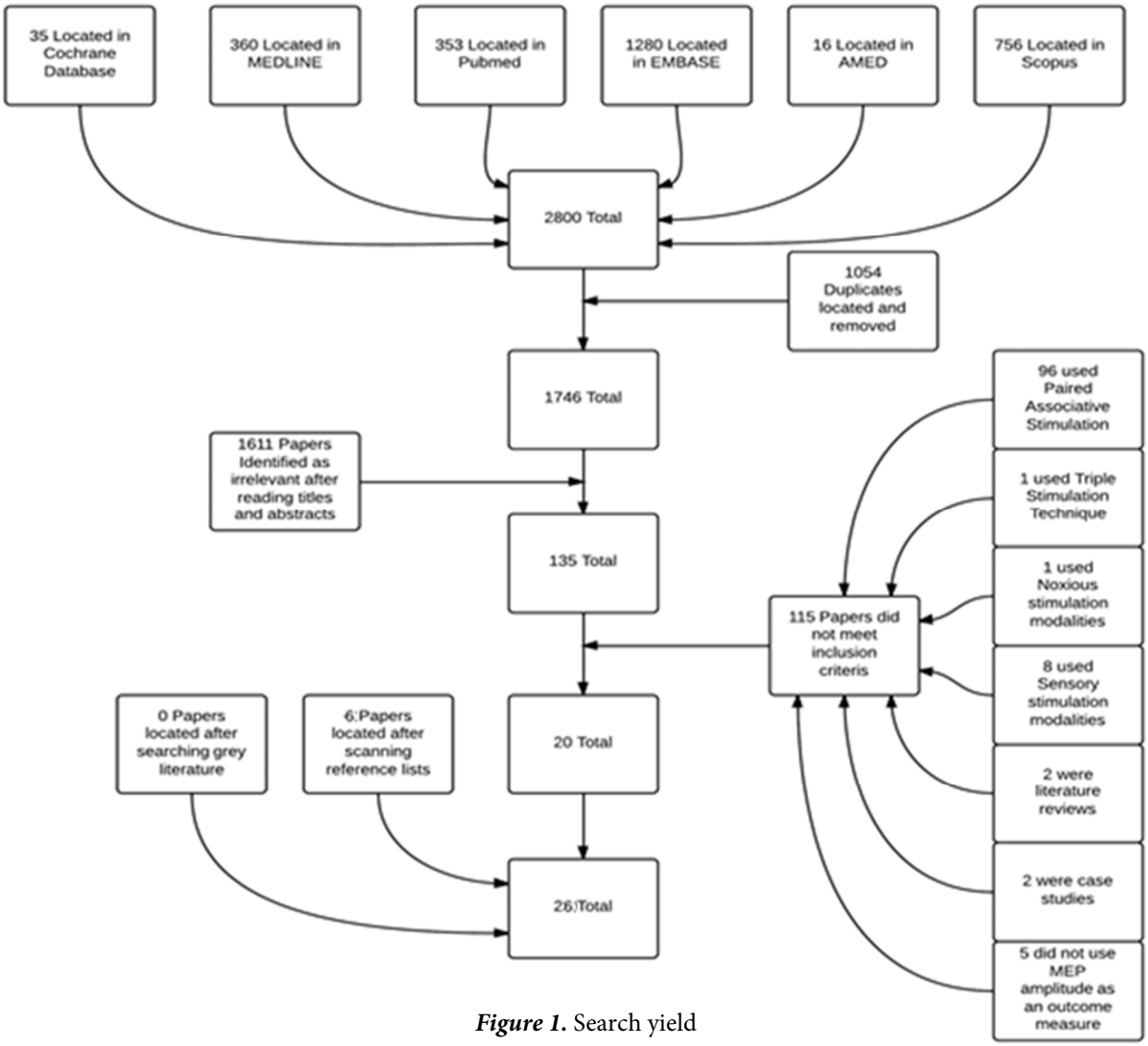

Figure 1. Search yield

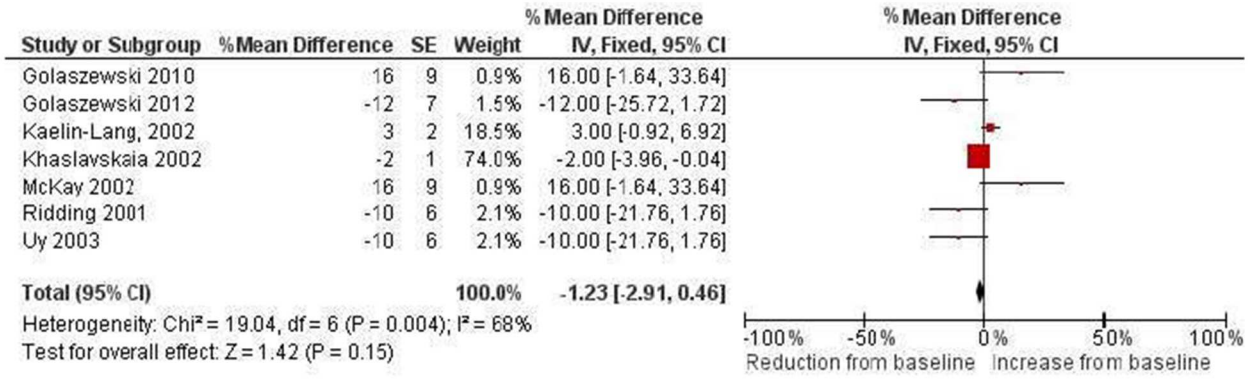

Figure 2. Meta-analysis of control data. N.B where SE was not provided, a conservative estimate was obtained based on significance levels reported in the paper

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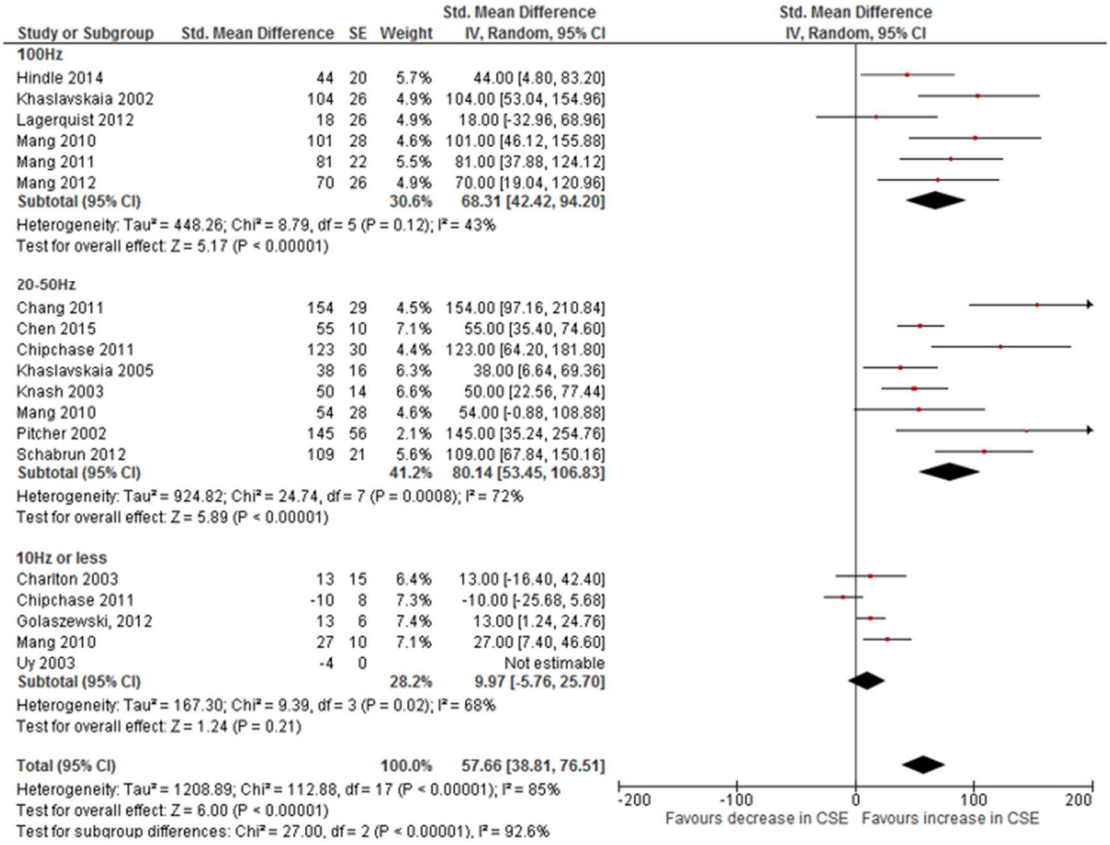

Figure 3. Meta- analysis of Motor Level Simulation data in healthy participants

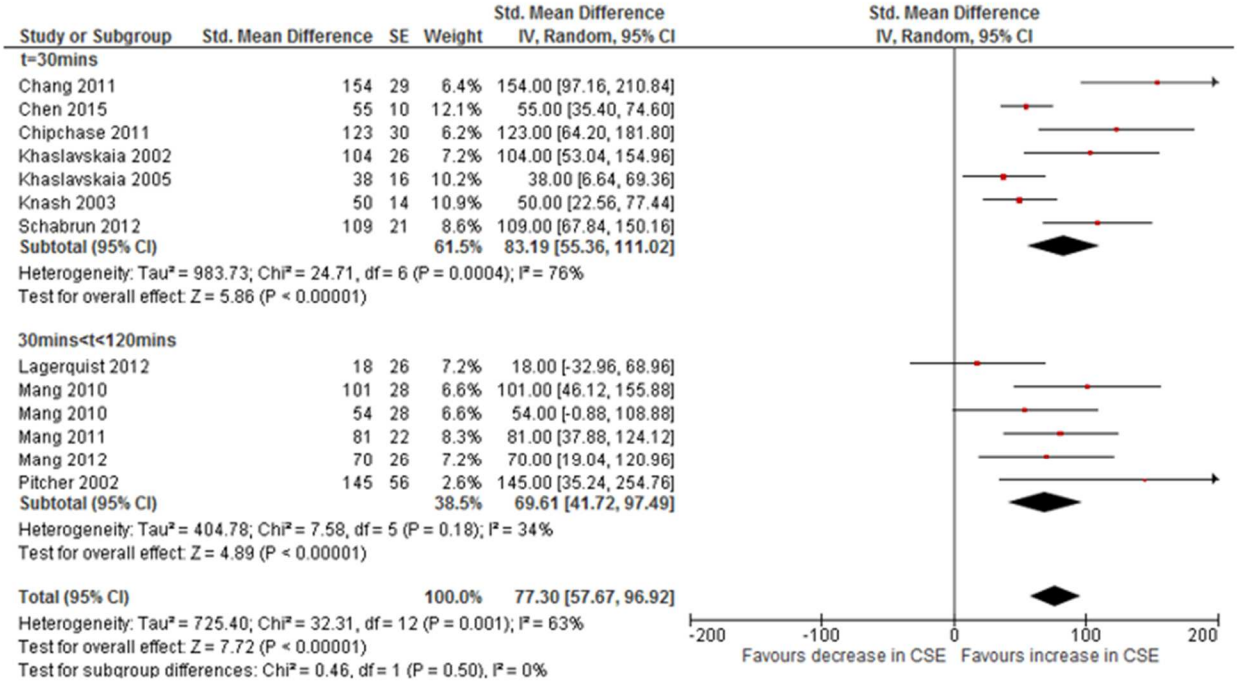

Figure 4. Meta- analysis of Motor Level Simulation at 20Hz or above, grouped by intervention time

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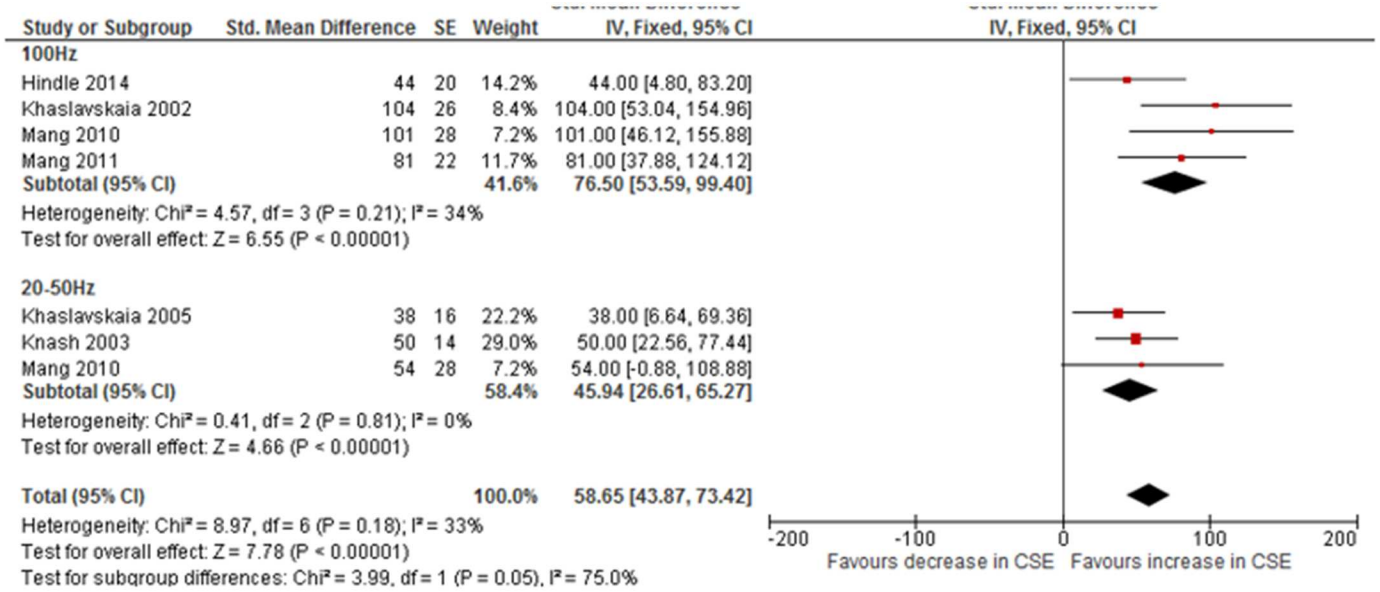

Figure 5. Meta- analysis of Motor Level Simulation of the CPN, grouped by frequency

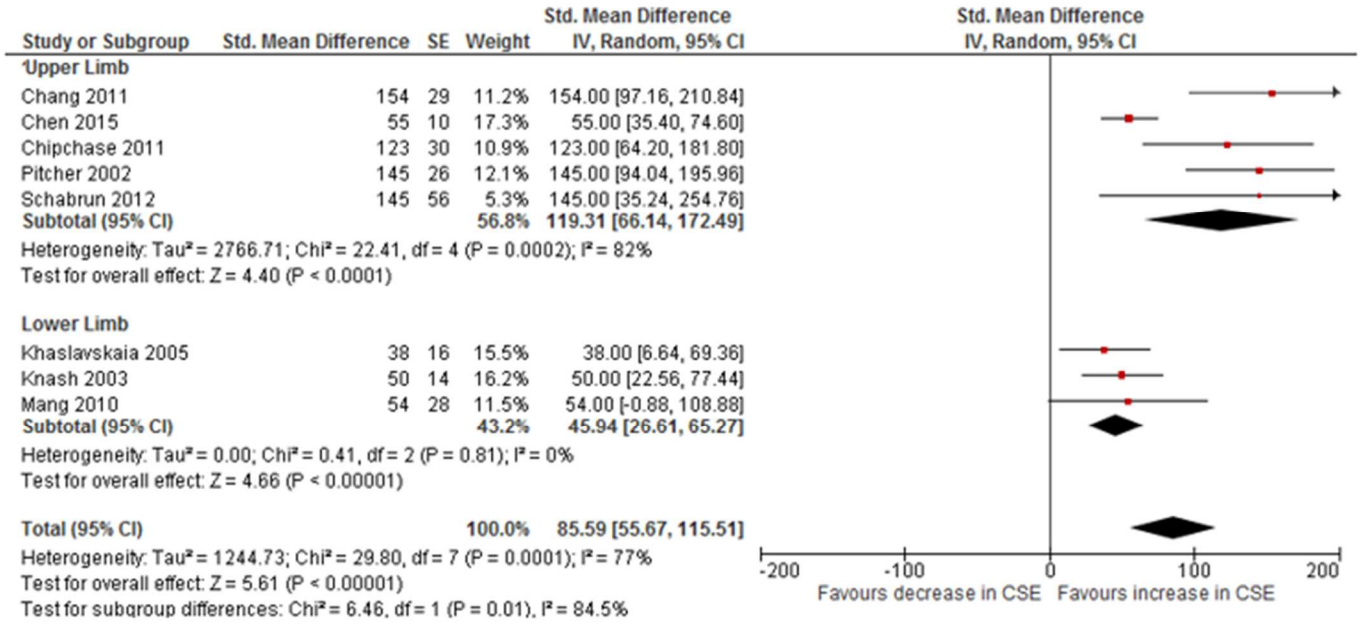

Figure 6. Meta- analysis of Motor Level Simulation of the CPN, grouped by stimulation location

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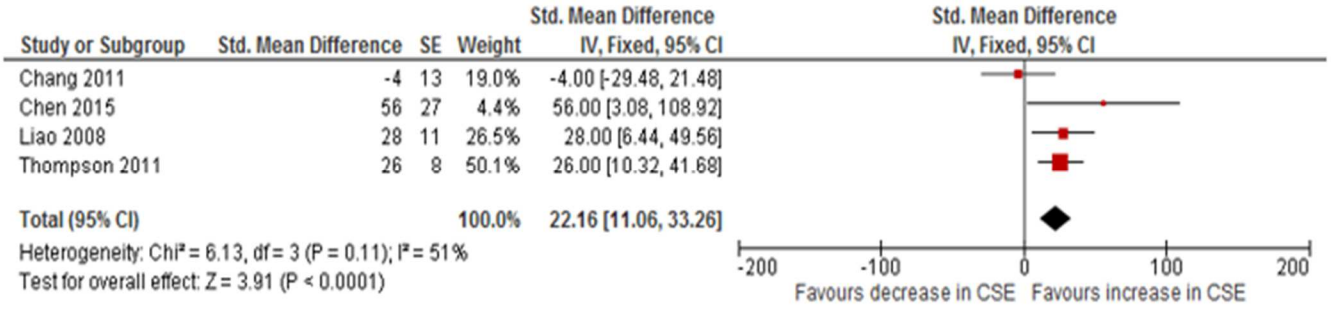

Figure 7. Meta-analysis of Motor Level Simulation data in neurologically impaired participants

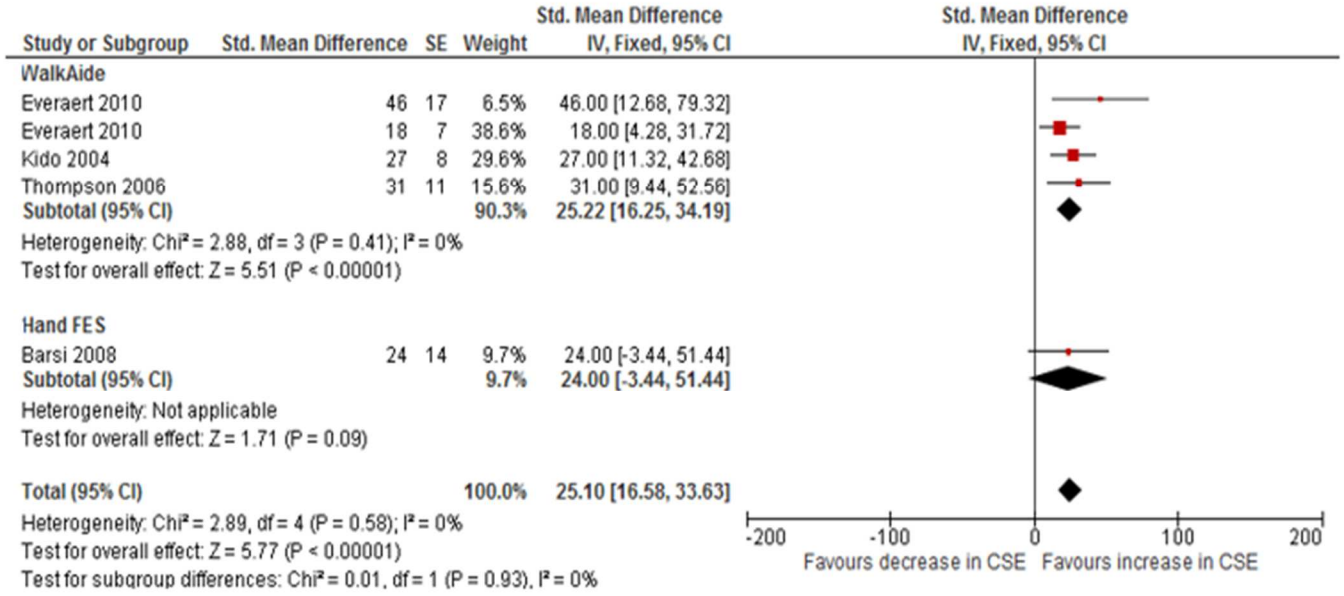

Figure 8. Meta-analysis of Functional Simulation Data

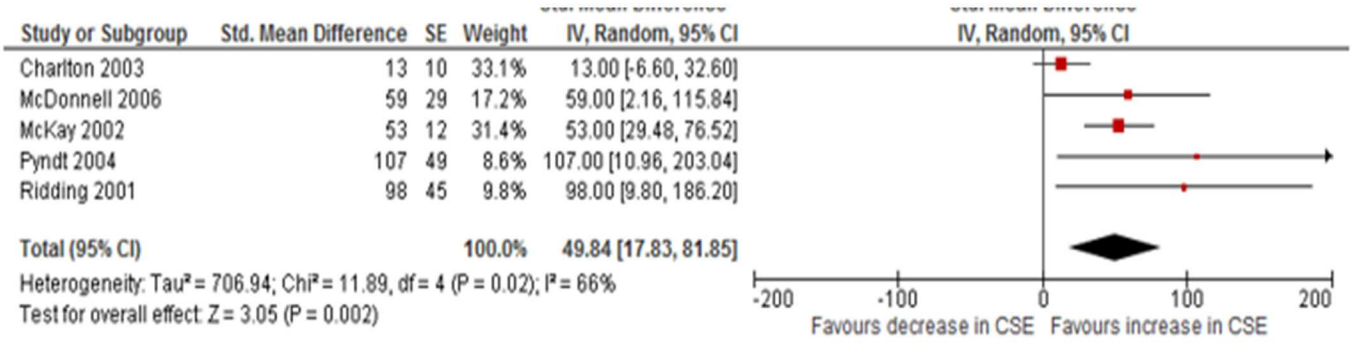

Figure 9. Meta-analysis of Associative Simulation Data

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reported within group statistics. 'Similarity at baseline' and 'treatment or control as allocated' was assured due to the nature of pretest-posttest trial designs. Whether or not the paper reported how from how many participants key outcome measures were obtained separated papers receiving a four from those receiving a five.

Control Data

Papers that included a sham/no stimulation group were identified and the percentage change from baseline was extracted to validate the use of pretest-posttest trial designs in the study (Table 3).

None of the papers reported significant differences in MEP amplitudes[26-32]. The meta-analysis revealed no significant difference: the mean difference was observed to be -1.23% (95% CI -2.91 to 0.46) (Figure 2).

Assessment of CSE

MEPs were measured at TA[29, 33-38], Flexor Carpi Radialis (FCR)[39, 40], first dorsal interosseous of the hand (FDI)[27, 32, 41-43], Soleus (SOL) [25], Flexor Hallucis Brevis [44], Abductor Pollicis Brevis [45], and biceps brachii [46]. The percentage change from baseline was extracted from MLS groups at too different time points, together with stimulation frequency, duration of intervention, and other parameters for studies with healthy participants (Table 4).

There was a significant heterogeneity in this data (Chi2 = 112.88 *P*<0.00001 I2=85%). A random effects meta-analysis revealed a significant change from baseline: the mean difference was observed to be 50.78% (95% CI 32.67 to 68.88) (Figure 3).

A subgroup analysis showed a significant change in the 100Hz subgroup with the mean difference to be 68.31% (95% CI 42.42 to 94.20) and in the 20-50Hz subgroup with the mean difference of 80.14% (95% CI 53.45 to 106.83), but not in the <10Hz subgroup with the mean difference of 9.97% (95% CI -5.75 to 25.70) (Figure 3). Further subgroup analysis showed that change in amplitude was greater where intervention time was 30 mins [mean difference: 83.19% (95% CI 55.36 to 111.02)], and then where intervention time >30 mins [mean difference: 69.61% (95% CI 41.72 to 97.49)] (Figure 4).

Analysis of CPN stimulation showed that stimulation at 100 Hz resulted in a greater mean increase [mean difference: 76.50% (95% CI 53.59 to 99.40)] than at 20-50 Hz [mean difference: 45.94% (95% CI 26.61 to 65.27)] (Figure 5).

At 20-50 Hz, upper limb representations showed a more significant increase [mean difference: 119.31% (95% CI 66.14 to 172.49)] than lower limb representations [mean difference: 45.94% (95% CI 26.61 to 65.27)] (Figure 6).

Motor Level Stimulation in Neurologically Impaired Participants

Only four papers looked at MEP amplitude changes in neurologically impaired individuals (Chang et al., 2011; Chen et al., 2015; Liao et al., 2008; Thompson et al., 2006). A meta-analysis demonstrated a significant change from baseline, although it was smaller in the healthy participant trials with the mean difference of 22.16% (95% CI 11.06 to 33.26) (Figure 7).

Functional Electrical Stimulation

Papers examining the effect of FES [6, 47-49] are tabulated in Table 5.

A meta-analysis revealed significant changes in baseline amplitude (mean difference: 25.10%) (95% CI 16.58 to 33.63) % (Figure 8). This data was homogenous (Chi2= 2.89 p = 0.58 I2=0) (Figure 8).

Associative Stimulation

Papers examining the effect of AS[17, 30, 31, 41, 50] are tabulated in Table 6.

All the experiments employed simultaneous stimulation of the radial and ulnar nerves. There was significant heterogeneity: Chi2=11.89 *P*=0.02 I2 = 66%. A meta-analysis revealed a significant change in baseline amplitude with the mean difference of 49.84% (95% CI 17.83 to 81.85) (Figure 9).

Functional Outcomes

Only five experiments in four papers examined functional outcome measures [6, 25, 44, 50] (Table 7). The outcomes examined include: maximum voluntary contraction[6, 25]; walking speed[6]; daytime urination frequency, nocturia frequency and pads/pay (n=1)[44], and Grooved Pegboard Test completion time[50]. All the experiments that reported significant increases in MEP amplitude reported an increase in respective functional outcomes as well. Lagerquist et al. (2012) did not report a significant increase in MEP amplitude, nor was an associated increase in torque production[25].

Discussion

The present review was conducted to summarize 26 trials, involving 394 participants, in order to examine the effects of electrical stimulation above motor threshold on peak-to-peak amplitudes of MEPs. The results indicated that MEP amplitude can be augmented by peripheral stimulation; however, the magnitude of change depends on the two stimulation parameters: frequency and duration. Further, it appears that different muscle groups respond differently to different frequencies.

Limitations

The current review study did not include papers published in languages other than English. It is possible that there is a wealth of literature in other languages that could add to our knowledge base in this topic, and future reviewers would benefit from an international or multilingual collaboration.

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All studies included in the present review recruited small samples (14 6.8). Although basic research frequently employs smaller samples to prove concepts, it creates wide confidence intervals and limits the generalizability of findings to other clinical situations. Furthermore, the translatability of the findings of review studies to a clinical setting is limited by the majority of studies exploring the effect of stimulation in healthy participants.

All the studies included tested the effects of treatment using time series designs. This trial design normally introduces a potential for bias due to the lack of control, making it impossible to determine whether the observed changes were the results of the intervention, or any number of confounding factors. Therefore, the present review was conducted to see whether MEP amplitude changes with either time or repeated measures using TMS and if time series designs are appropriate for this area of research.

Trial Design

Five papers were identified in which sham stimulation was performed by replicating the experimental protocol with 0 mV intensity (Table 3). Two additional studies included 'no-stimulation' experiments as part of a repeated measures design. Despite three studies reporting a slight increase[26, 28, 30] and four others reporting a slight decrease[27, 29, 31, 32] none of the control groups showed statistically significant deviations from baseline in MEP amplitude. Further, a meta-analysis of the abovementioned studies revealed no significant pooled difference (Figure 4). The slight decrease in CSE observed may be a consequence of a period of inactivity dictated by the sham protocol. These results support the validity of using baseline scores as controls where MEP amplitude is the outcome measure.

Motor Level Stimulation

A total of 19 experiments examined the effect of MLS on MEP amplitude in healthy individuals (Table 4). Of these, 13 reported significant results. There was significant heterogeneity within the data (Figure 3), possibly resulting from the use of a variety of stimulation parameters and differences in participant characteristics. Nonetheless, a random effects analysis confirmed that this intervention results in a significant increase in MEP amplitude (Figure 3). A sub-group analysis of this data focusing on differences in stimulation frequency, explains some of the inconsistency in the findings.

From among five trials conducting MLS at frequencies of 10Hz or less (Table 4), only one demonstrated significant change from baseline (Figure 3). This indicates that MLS needs to be performed at frequencies greater than 10Hz to affect CSE.

Also, eight experiments used frequencies between 20 and 50Hz (Table 4). While the reported MEP amplitude change from baseline varied between studies, they were unequivocal in their support for the hypothesis that electrical stimulation increases CSE. This contention was echoed by the results of a meta-analysis performed by the present author (Figure 3). It is worth noting that the observed heterogeneity may be attributable to disparities in regions tested.

Moreover, six experiments were performed at 100Hz (Table 4). A meta-analysis revealed a significant increase in MEP amplitude (Figure 3). All the experiments performed at the CPN at this frequency were consistent with this finding. Conversely, Lagerquist *et al.* stimulated the tibial nerve at 100Hz, measuring MEPs at SOL, and found little change in amplitude resulting from stimulation. The authors proposed that the lack of MEP modulation was due to SOL being under less cortical control than TA, with a much smaller cortical representation. So, while stimulation above 100Hz produces significant increases in excitability of the cortical representation for TA, it does not appear to be universal, and highlights the need for further specific research into the effects of electrical stimulation at different frequencies in different muscle groups.

Of all muscles, TA has been the most studied. Stimulation of the CPN at 20-50Hz produces significant increases; however, stimulation at 100Hz appears to yield better results (Figure 5). Conversely, upper limb representations respond better than lower limb representations to frequencies of 20-50Hz (Figure 6). This demonstrates that research findings relating to the effect of MLS cannot generally be extrapolated to any given muscle or nerve to support clinical use as different areas respond differently to a range of frequencies. However, it appears that 10Hz is insufficient to produce changes in any of the tested muscle groups. This is in keeping with the conclusions drawn by Heynen *et al.* who studied the effect of stimulation at different frequencies in an animal model[51]. They found that stimulation at high frequencies (100Hz) induced LTP and stimulation at low frequencies (1Hz) produced long term depression, while stimulation at 10Hz produced no lasting results. It is possible that 10Hz stimulation lies between the ideal frequencies for facilitating and depressing excitability and may produce either effect depending on participant characteristics, resulting in an insignificant mean difference. Moreover, MLS at low frequencies does not produce tetany, and as such does not simulate a physiological movement not does it provide normal physiological proprioceptive feedback to the CNS. This may in part explain lack of CS modulation with this stimulation parameter.

A secondary aim of the present review was to examine whether changes in MEP induced by peripheral stimulation also correlate with functional outcomes. This aims to expand on the work of Heald *et al.* In a longitudinal study, they showed that the size of post stroke MEPs correlates positively with clinical recovery [52]. Three experiments investigated the correlation between cortical and functional changes, where MLS was used as the intervention. The patient profiles, areas stimulated, and functional outcomes recorded were extensively different. On examining the effect of sacral root stimulation in incontinent patients, Liao *et al.* reported a significant increase in MEP amplitude alongside a significant reduction in continence outcomes (Table 6). McDonnell and Ridding found that radial and ulnar AS increases not only FDI representation excitability

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but also the speed of completion of a complex sensorimotor training task (Table 6). Lagerquist *et al.* reported no change in Maximum Voluntary Contraction torque (MVC) of SOL alongside minimal change in CSE (Table 6). This finding suggests that modulation of MEP amplitude can translate into changes in clinical outcomes. However, there is no evidence that these findings can be generalized beyond the outcomes they have measured. Future research into electrical stimulation should endeavor to examine both functional and electro-neurophysiological measures to confirm translatability.

There is paucity in the literature exploring the effect of MLS on a neurologically impaired cohort, with only four papers identified for the current review (Table 4). Chen *et al.* studied the effect of median nerve stimulation on FDI excitability in patients with spinocerebellar ataxia and demonstrated a significant increase in CSE [40]. Chang *et al.* examined the effect of FCR stimulation in spinal cord injury and showed no MEP modulation [39]. Liao *et al.* studied the effect of sacral root stimulation in incontinent patients revealing significant increase in MEP amplitude (Table 4). Also, Thompson *et al.* considered the effect of CPN stimulation in patients with incomplete spinal cord lesions and showed a significant increase in MEP amplitude (Table 4). While a meta-analysis showed a small but significant increase in MEP amplitude from the baseline (Figure 7), the areas stimulated and the impairments considered varied significantly. While MLS shows promise for enhancing CSE in neurological rehabilitation, there is currently insufficient evidence to support its use. In particular, there have been no studies looking at the effect of peripheral stimulation on CSE in stroke or Traumatic Brain Injury rehabilitation. Future research should aim to elucidate whether findings in a healthy cohort can be translated to neurological patients, as such interventions could have the most impact in this population.

Functional Electrical Stimulation

From among the five papers testing the effects of FES on MEP (Table 5), four used a foot-drop stimulator. The results of these studies homogenously supported a significant increase in CSE (Figure 8). Everaert *et al.* examined the use of the Walk-aide system for several months in both progressive and non-progressive neurological conditions. The authors demonstrated not only an increase in MEP amplitude in both progressive and non-progressive conditions (Table 5) but also an increase in MVC in both groups (Table 7). Moreover these changes translated to improvements in walking speed measured with Walk-aide off (Table 7). While traditionally FES has been considered to have primarily an orthotic effect, these results demonstrate that, using a foot drop stimulator, neurologically impaired patients can develop superior voluntary control of TA, which translates to increased walking speed. Yet, Barsi *et al.* failed to show similar increases with hand FES (Table 5). However, when the electrical stimulator augmented voluntary contractions, a significant increase was observed in CSE (37 16%). This suggests that the intention to activate the muscle has a role to play in modulation of CSE by FES.

Associative Stimulation

It has been proposed that two electrical stimuli delivered together (AS) may result in superior modulation of CSE. Five studies tested an associative protocol stimulating the radial and ulnar nerve simultaneously (Table 6). All AS trials used 10Hz as the stimulation frequency. In contrast to non-associative protocols, stimulation at this frequency produced significant increases in MEP amplitude (Figure 9). However, this increase was smaller than that found in MLS studies where frequencies were greater than 20Hz. In a clinical setting, it is easier to set up higher frequency of a single nerve than implementing an associative protocol.

Intervention time

Associative stimulation studies that used an intervention time of 60mins produced consistently better results than those that stimulated for twice as long (Figure 9). This is congruent with the data for MLS, where the mean change from baseline was greater when stimulation lasted for 30mins than when it exceeded 30mins (Figure 4). While it is possible that longer durations of stimulation may produce more lasting results, it is clear that at least in the short term, longer duration does not translate to larger increases. Pitcher and Miles showed that in some individuals, electrical fatigue resulted in a depression of CSE. This could explain why shorter durations of stimulation produce on average more significant facilitation. This suggests that shorter but more frequent bouts of stimulation, not resulting in fatigue, may be clinically more useful. To bring an evidence base for electrical stimulation protocols into clinical practice, future research should be directed at determining appropriate intervention duration to produce both the greatest and the longest lasting plastic changes.

Previous Review

Another systematic review of stimulation parameters across all stimulation intensities was recently published[24]. Several papers are included in the current review that were missed in the previous one. Additionally, several papers have been published since then. Chipchase *et al.* reported only whether MEP amplitude increased or decreased in other studies and failed to report the amount and significance of the changes[24]. Corollary to this, only 10 experiments were included in their meta-analysis, with no sub-group analysis performed to compare stimulation parameters. Moreover, their conclusions as to the effect of different stimulation frequencies on CSE were contrary to those found in the present study. This was due to a smaller number of papers included, lack of subgroup analysis, use of different frequency brackets (<25Hz, 30-50Hz, >90Hz), and lack of differentiation between sensory and MLS intensities in considering the effect of frequency.

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Conclusion

The present review conclusively shows that peripheral electrical stimulation above motor threshold can increase CSE in healthy individuals. It is apparent that stimulation frequency is a major determining factor as to whether this occurs, and to what extent. It also appears that different areas respond differently to various frequencies. The CPN has extensively been studied and it has been established that the representation of TA responds best to frequencies of 100Hz. Additionally, FES of the TA has been shown to produce changes in CSE that translate to better voluntary control. Upper limb representations, especially those related to hand function, respond well to frequencies of 20-50Hz; however, there have been limited studies examining the effect of 100Hz stimulation in the upper limb, and this may prove to be more effective. More research, with larger sample sizes, should be conducted to determine appropriate frequencies for specific muscle groups. As MEP amplitude does not change simply based on repeated measures using TMS, in the future research all available participants should be placed into an experimental group to produce the most significant findings. Literature relating to modulation of CS pathways in neurologically impaired individuals is even scarcer. As this intervention has the potential to be most useful in this cohort, there is a need for more research relating to modulation of excitability in neurological conditions to establish efficacy in neurological rehabilitation. Another area where research is needed is the appropriate duration and frequency of intervention required to produce the most significant and lasting changes. It appears as though electrical fatigue may result in depression of pathways and shorter treatment times produce more significant facilitation; however, it is unclear how often the intervention should be provided to produce the most lasting changes. This will enable the development of evidence-based treatment protocols.

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