This analytic review reports how prolonged periods of somatosensory electric stimulation (SES) with repetitive transcutaneous nerve stimulation can have ‘direct’ and ‘crossed’ effects on brain activation, corticospinal excitability, and motor performance. A review of 26 studies involving 315 healthy and 78 stroke and dystonia patients showed that the direct effects of SES increased corticospinal excitability up to 40% (effect size: 0.2 to 6.1) and motor performance up to 14% (effect size: 0.3 to 3.1) but these two features did not correlate. SES did not affect measures of intracortical excitability. Most likely, a long-term potentiation-like mechanism in the excitatory glutamatergic connections between the primary sensory and motor cortices mediates the direct effects of SES on corticospinal excitability and motor performance. We propose two models for the untested hypothesis that adding SES to unilateral motor practice could magnify the magnitude of inter-limb transfer. If tenable, the hypothesis would expand the evolving repertoire of sensory augmentation of cross-education using mirrors and add SES as an alternative to conventional rehabilitation strategies such as constraint-induced movement therapy.
2.1 INTRODUCTION

Sensory inputs are necessary for the successful execution and acquisition of skillful voluntary movements. Stimuli from the environment activate skin, pain, temperature, pressure, tendon, and muscle receptors that provide feedback for, for example, finger movements while typing, monitoring the position of the arm in space during reaching, and fine tuning facial expressions [1-5]. Sensory inputs are also required for learning motor skills [6-9]. In contrast, patients with dysfunctional peripheral sensory receptors execute voluntary movements inaccurately or in severe cases are unable to grasp a pen, write, and fasten shirt buttons with one hand [10-12]. Primates with ablated somatosensory cortex have great difficulty in learning to catch a falling food pellet [13] and somatosensory deficits caused by an ischemic stroke interfere with the recovery of voluntary movements [14-16].

The empirical and clinical observations concerning the key role of sensory inputs in motor function gave rise the hypothesis that augmenting sensory inputs through somatosensory electrical stimulation (SES) could perhaps improve function and reduce weakness by enhancing the excitability of the neuronal path projecting to muscles and joints wherein the sensory receptors are stimulated [17-23]. However, the mechanism of how, if at all, SES increases motor function is incompletely understood. While transcranial magnetic brain stimulation (TMS) and imaging studies report consistent increases in the excitability of the primary motor (M1) and sensory (S1) cortices and other elements in the sensorimotor network (see below), such changes do not always improve motor function (cf. [24] as many studies report actually reductions in motor excitability after SES [25-29]). In addition, the optimal SES parameters (duration, intensity, frequency) for modulating plasticity in M1 and S1 are unclear and there is also ambiguity if the parameters that increase neuronal excitability also improve motor function. Although the direct effects of SES are focal within, for example, the hand area, there is also evidence that SES can give rise to effects that cross to remote brain areas in particular to contralateral homologous structures [30-33].

Targeting neurologists, physical therapists, and other rehabilitation experts, the present narrative review provides an integrative analysis of the direct and crossed effects of electrical SES on neuronal excitability and motor function. Here we consider a form of SES that could be used in a clinical setting to improve motor function and define it as painless, low frequency and prolonged (≥ 20 minutes) transcutaneous electrical stimulation of a peripheral nerve or motor point at current intensities below, at, or just above motor threshold [24]. The hypothesis is that such SES modality would increase corticospinal and motor cortical excitability, and brain activation, and also produce improvements in motor function in healthy individuals or in patients who suffer from a motor dysfunction. The hypothesis focuses on the motor brain due to minimal data on the effects of SES on spinal excitability in upper extremity muscles. First, we review the neuroanatomical paths that convey sensory signals to target motor areas in the brain. Second, we analyze the mechanisms of how SES increases corticospinal and M1 excitability and review how SES parameters affect corticospinal and M1 plasticity. Third, we examine the association between changes in corticospinal and M1 plasticity (cf. [34] and the ensuing changes
in motor function. Finally, we present models for the direct and crossed effects of SES. Within the conceptual framework of cross-education [35-41], we propose the untested and provocative hypothesis that adding SES to unilateral motor practice could magnify the magnitude of interlimb transfer. If tenable, the hypothesis would expand the evolving repertoire of sensory augmentation of cross-education [38,41] and provide alternatives to conventional methods such as constraint-induced movement therapy [42] which are not suitable for patients with a unilateral orthopedic injuries [43-46].

To reduce variation between studies in methods and subjects, the analysis includes studies that used prolonged SES in the form of electrical stimulation, functional electrical stimulation, peripheral nerve stimulation, electrical nerve stimulation, and paired associative stimulation (PAS) directly to a peripheral nerve or to the motor point of an upper extremity muscle. PAS, which we consider here as a form of SES, combines peripheral electrical nerve stimuli with magnetic pulses delivered to the motor cortex with specific interstimulus intervals and intensities [47]. We included PAS with the understanding that it produces heterotopic plasticity presumably through associative long-term potentiation [48]. In contrast, other forms of SES, using electrical-only stimuli, produce homotopic plasticity (Table S1). Because of this important difference, we analyzed PAS as a separate form of SES. We did not consider studies designed to probe the immediate (> 1 s) effects of single cutaneomuscular stimuli on the motor brain [25-29,31,49]. We excluded electrical muscle stimulation that produces strong muscle contractions in the form of neuromuscular electrical stimulation [50], uses high frequency transcutaneous nerve stimulation to manage pain [51], and studies targeting lower extremity muscles [52-55]. We also excluded mechanical vibration from the analysis because of its unique nature as a sensory stimulus [56]. Using such inclusion criteria, we found that the effects of SES on corticospinal excitability were tested in healthy participants only in the age range of 25.5 – 36.5 years without testing motor performance. In contrast, the studies that determined changes in motor performance used only patients and did not measure changes in neuronal excitability. These latter studies uniformly showed improvements in motor performance. “Direct” effects produced by SES are those that modulate the excitability of spinal, corticospinal, and cortical structures associated with the site of stimulation, whereas “crossed” effects are those that modulate the excitability of the contralateral structures not targeted by the direct effects.

2.2 DIRECT EFFECTS OF SES MODULATE MOTOR EXCITABILITY

2.2.1 Neuroanatomical basis of how SES modulates motor excitability

Non-painful SES at near-motor threshold intensity excites group la primary large muscle afferents, group Ib afferents from Golgi organs, and group II afferents from slow and rapidly adapting skin afferents, as well as secondary muscle afferent fibers [57,58]. Neuroanatomical, electrophysiological, and imaging data suggest that SES affects the excitability of the contralateral S1, supplementary motor area, dorsal premotor cortex, posterior parietal cortex, M1, and ipsilateral cerebellum and bilateral S2 [59-67]. Most likely corticocortical connections mediate the effects of peripheral SES on M1 because the number and strength of the direct connections between peripheral sensory receptors

19
on one side of the body and the contralateral M1 are few and weak [68-71]. For the upper extremity, the sensory volley ascends in the dorsal medial lemniscus to nucleus cuneatus in the medulla oblongata and after crossing, sensory signals enter the ventral posterolateral nucleus in the rostral thalamus and project to S1 (Brodmann areas 1, 2, 3a, 3b, and 4) and S2 (Brodmann areas 40 and 43) [72-74]. There are direct connections between areas 1 and 2 of S1 and M1 [69,70,75,76], between S2 and M1 [70], and between areas 5 and 7 of the posterior parietal cortex and M1 [70,77] within the same hemisphere, making it possible for SES to affect M1. These connections seem to be somatotopically organized in mammals [76,78], including humans [79] so that the same body parts are connected between S1 and M1. Sensory signals from S1 reach pyramidal tract cells, the motor cortical output cells, in layer V through monosynaptic connections or via oligosynaptic connections, with interneurons relaying the signals in layers II and III [80,81]. Severing these connections within the same hemisphere impairs motor function in primates [82]. With parameters used in human studies, activation of the neurons in the sensorimotor thalamus and S1 can induce long-term potentiation in M1 via excitatory glutamatergic synapses [83,84] and can increase the synaptic density in M1 [85]. SES can modulate cerebellar excitability and in turn affect the activity of S1-M1 connections via the ventrolateral thalamic nuclei because hemicerebellectomy in rats prevents the SES-induced increase in M1 excitability [65,86]. We note that there are reciprocal effects from M1 to S1 via direct corticocortical connections that can modulate the state of S1 [117].

2.2.2 SES modulates corticospinal excitability

To the best of our knowledge, there are no studies that examined spinal reflexes in upper extremity muscles after prolonged SES. SES does not affect the amplitude of maximal compound action potential, F-wave amplitude and its persistence, and the responses to electrical brainstem stimulation [57,87].

2.2.2.1 Effects of SES location and frequency

Non-painful forms of SES that produce minimal or no muscle contraction can decrease or increase corticospinal excitability. SES of the median nerve at ~100 Hz for 40 minutes at motor threshold intensity increased corticospinal excitability approximately 56% (p < 0.05; effect size: 1.31) as estimated by the amplitude of the motor evoked potentials (MEP) in the abductor pollicis brevis [88]. SES of the ulnar nerve at ~10 Hz for 120 minutes at around motor-threshold intensity increased corticospinal excitability 82% (p < 0.05; effect size: 1.00) in the first dorsal interosseous [87] and the abductor digiti minimi [58]. SES of the radial and ulnar nerves simultaneously at 10 Hz for 120 minutes at motor threshold intensity increased corticospinal excitability 74% (p < 0.05; effect size: 6.1) in the first dorsal interosseus [89,90]. On average from all the relevant studies, SES of a peripheral mixed nerve increased corticospinal excitability 73.5% (±22) in 150 healthy young males and females (five studies).

When SES targeted a motor point instead of a motor nerve, the changes in corticospinal excitability were smaller and less consistent (Table S1, online supplement). SES to the biceps brachii for 30 minutes at below-motor threshold intensity at 10 or 100 Hz [91] and to the abductor pollicis brevis at 100 Hz [92] decreased corticospinal excitability 45, 50, and 69% (all p < 0.05; effect sizes: 0.87, 0.70, and 2.60), respectively, in 25 healthy young
participants. In contrast, concurrent SES of the first dorsal interosseus and abductor pollicis brevis [93] (3.5 Hz, 60 minutes), biceps brachii [91] (10 or 30 Hz), and first dorsal interosseus [89] modified corticospinal excitability 68, -10, 125, and 50% (effect sizes: 1.01, 0.50, 0.82, non-computable), respectively in 36 young participants.

PAS (interstimulus interval, 25 ms) with the peripheral stimulus targeting the median nerve [48,94,95], radial and ulnar nerve [96], extensor carpi radialis [97], and first dorsal interosseus [98-100] at 7 Hz for 31 minutes at just-below motor threshold intensity increased corticospinal excitability 64% (p < 0.05; effect size range: 0.50 to 5.7) in 121 healthy young participants. PAS (interstimulus interval of 25 ms, peripheral stimulus 0.1 ms pulse duration), targeting the first dorsal intersseus muscle motor point also produced bidirectional effects; trains of SES, delivered every 10 s to the first dorsal interosseus motor point at 3 Hz (two pulses per 660 ms train) or 30 Hz (20 pulses per 660 ms train), respectively, depressed and increased corticospinal excitability [99]. The authors explained this bidirectional effect by SES strengthening or weakening synaptic connections in a frequency-dependent manner through long-term potentiation or depression-like mechanisms, respectively.

For all SES protocols, there is also large between-subject variation so that 25% of participants showed depression while other subjects showed MEP facilitation after the same protocol [89]. Overall, SES delivered, respectively, to a peripheral mixed nerve compared with a motor point, increased corticospinal excitability 7-fold more, 74% (±22) versus 10% (±72), whereas PAS increased corticospinal excitability 61% (±50). The large effect is probably due to nerve but not the motor point stimulation activating the sensory fibers.

### 2.2.2.2 Effects of SES intensity

We examined the association between SES intensity and corticospinal excitability by categorizing SES into sub-sensory, low sensory, high sensory, and low motor intensity in relation to perceptual or motor threshold. Corticospinal excitability seems to be sensitive to SES intensity because the effects ranged between depression and facilitation of the TMS-generated MEPs. SES delivered at a high sensory intensity (i.e., two times perceptual threshold) increased corticospinal excitability 34% (range -0.18 to 68%; effect size range: 0.0 to 1.0) [58,101] but low sensory stimulation at a high frequency (55 Hz) decreased corticospinal excitability as much as 42% (effect size range: 0.2 to 2.6) (Figure 2.1) [91,92,102]. PAS (interstimulus interval 25 ms) at high sensory intensity at a frequency of 0.1 Hz increased corticospinal excitability 60% (p < 0.05; effect size range: 1.0 to 5.2) [48,94,95], whereas PAS at an intensity just above motor threshold at a frequency of 10.5 Hz increased corticospinal excitability 66% (p < 0.05; effect size range: 0.5 to 3.13) [90,96-99]. Because no study has systemically manipulated frequency and intensity, we can only assume an interaction between these two factors.

### 2.2.2.3 Effects SES duration

Concerning the duration of SES, previous studies found that corticospinal excitability peaked and function in low back patients improved after 30 to 60 minutes after SES [98,103]. We also found an association between SES duration and changes in
Figure 2.1. Somatosensory electrical stimulation (SES) increases corticospinal excitability and motor performance. Panel A. Association between duration of SES of a motor nerve or a muscle thorough a motor point at a frequency 0.1 to 100 Hz and intensity ranging between below perceptual threshold and just-above motor threshold and changes in MEP size. The equation \( y = -0.05x^2 + 8.5x - 248.9 \), \( R^2 = 0.83 \) describes the relationship. A log-transformation of the data does not affect the relationship. Panel B. Effects of SES intensity on corticospinal excitability (filled columns; data from 1, 4, 2, and 7 studies per intensity category) and motor performance (open columns; data from 2, 2, 5, and 2 studies per intensity category). The four intensity categories, respectively, correspond to: Perceptual threshold (PT), twice PT, three times PT, and at motor threshold. Panel C. Effects of SES frequency on corticospinal excitability (8 studies for \( \leq 10 \) Hz and 3 studies for \( \geq 10 \) Hz). There are insufficient data to plot the effects of SES frequency on motor performance. For Panels A-C, data are pooled from 26 studies, including 315 healthy and 78 stroke and dystonia patients, mean age 36. Vertical bars denote standard deviations.
corticospinal excitability (data from 11 studies pooled for 115 healthy volunteers and for 31 stroke patients, $R^2 = 0.83$). This correlation analysis is complicated by the differences between studies in SES frequency as it ranged between 3.5 to 100 Hz with the stimulus delivered in a continuous form and trains [88,92,93] and by differences in SES intensity ranging between below-perceptual to just-above motor threshold [88,101,104]. Based on Figure 2.1 the emerging picture is that SES of a mixed nerve at a frequency < 10 Hz for 60-120 minutes at around motor threshold intensity is the most effective form to increase corticospinal excitability.

2.2.3 SES has little direct effects on intracortical M1 excitability

Although imaging [67,105] and EEG studies [106] suggest M1 involvement in response to prolonged SES, TMS experiments probing M1 excitability by double pulse paradigms consistently found no changes in GABA-mediated short-interval cortical inhibition (SICI) and the NMDA-mediated intracortical facilitation (ICF) after SES [58,101,102,107] and SES in the form of PAS [90,94,95,97,108]. For example, SICI was similar (p > 0.05) before (47%) and after (51%) prolonged continuous median nerve stimulation, as was ICF (159 vs. 186%) [58]. In addition, in PAS paradigms the 15 and 18% reductions in SICI (p > 0.05) could not explain the increase in M1 excitability [48,94]. We found no association between SES frequency (range: 0.05 to 10 Hz) and changes induced by PAS in SICI ($R^2 = 0.01$, five studies). Duration of PAS strongly correlated with reductions in SICI ($R^2 = 0.97$, five studies) and SES reduced SICI when it was delivered at low sensory (-38%) but not at high sensory (1%) and low motor (-1.3%) intensity (all p > 0.05). PAS reduced SICI when SES was delivered at high sensory (12%, 3 studies) and low motor (18%, 2 studies) intensities. The SES-induced changes in SICI correlated $R^2 = 0.11$ (four studies) with changes in corticospinal excitability for SES and $R^2 = 0.27$ (five studies) for SES in the form of PAS. Thus, SES most likely affects both measures to a different extent and through different mechanisms [109].

2.2.4 Mechanism of how SES modulates cortical and corticospinal excitability

Multiple lines of evidence suggest that the direct effects of prolonged SES produce lasting and spatially specific corticospinal plasticity. The most likely neuroanatomical paths through which SES increases corticospinal excitability are the connections between S1 and M1 [110-115]. Although SES activates the ventrolateral pars oralis and caudalis thalamic nuclei, which have inputs to M1, the somatosensory evoked potentials were stable during sustained SES of the ulnar nerve [58] and the caudal connections are known to be sparse and diffuse [116]. Therefore, thalamic inputs to M1 under such conditions probably play a small role. While connections from cerebellum and premotor areas could also affect M1 activation, imaging data suggest that prolonged SES produced task-related fMRI activation changes in M1 and S1 and little changes in dorsal premotor cortex [67,105,117]. In addition, SES displaced sensory representation of the thumb towards the other fingers within S1 and somatotopically increased perfusion and blood-oxygen-level-dependent signal voxel count (50% and 100%, respectively) and intensity (25% and 20%, respectively), suggesting a putative role for S1 in modulating M1’s output to the spinal motoneurons [67].
SES can increase corticospinal excitability at multiple sites. The increase in MEP amplitude after SES is probably not due to changes in the excitability of the muscle fiber sarcolemma, neuromuscular junction, and the soma or axon hillock of motoneurons because SES did not affect the maximal compound action potential, F-wave, and responses to brainstem stimulation [20,48,58,104]. Therefore, lasting increases in corticospinal excitability in response to SES probably occur at supraspinal and/or interneuronal levels [62,67,105,118-121].

An increase in maximal MEP amplitude at rest represents a change in the balance between excitation and inhibition resulting in increased excitability of descending paths [122]. Because prolonged SES of the mixed ulnar nerve shifted the input-output curve upward in response to TMS [58], prolonged SES most likely modulated the excitability of M1. The TMS responses and the S1-M1 connections are also somatotopically organized: corticospinal excitability increased in the ulnar nerve-innervated abductor digiti minimi but not in the median nerve-innervated control muscle [58,104]. Thus, the changes in corticospinal excitability induced by SES probably reflect an increase in M1 excitability. There is other evidence for SES being focal: the recruitment curves did not shift upward in hand and esophageal muscles when SES targeted pharyngeal muscles [20].

An unresolved issue is that pharmacological studies showed that SES probably involves GABA-ergic neurons in M1 [58] but, as reviewed in the previous section, SES does not modulate SICI [48,58,95,97,102,108,123], an index of intracortical inhibition mediated by GABA-ergic neurons. In other words, TMS data on corticospinal excitability, fMRI, and EEG data all seem to point to the conclusion that prolonged SES upregulates corticospinal excitability through M1 under most conditions but direct measures of intracortical excitability, i.e., SICI and ICF, do not capture these changes. One possibility is that SES does not affect interneurons accessed by SICI and ICF. Future studies will have to clarify if SES might induce subtle changes in SICI and if such changes are clinically meaningful.

The optimal combination of stimulation parameters causing the largest upregulation of corticospinal excitability is remains unknown [34]. Figure 2.1A-C show trends that SES at or below the motor threshold and below 10 Hz produced the most reliable (but not necessarily the greatest) increases in corticospinal excitability independent of SES duration. However, this summary requires caution because the data are from different studies and not the result of a systematic manipulation of SES parameters. For example, SES applied at 30 Hz for 30 minutes at low motor intensity can also increase corticospinal excitability 125%, whereas SES applied at 100 Hz for 30 minutes at low sensory intensity decreases corticospinal excitability 50% [91]. Nonetheless, at such intensities, SES of a mixed nerve activates both muscle and cutaneous afferents. Digit stimulation activates mostly cutaneous afferents. Cutaneous afferents project to areas 3b and 1 and muscle afferents project to areas 3a and 2 in S1 [69,124] and area 2 somatotopically connects to M1 [70]. Then, the most likely pathways that mediate changes in corticospinal excitability involve deep proprioceptors and deep cutaneous receptors without exciting nerve endings of C fibers, thereby giving rise to a relatively direct and pain-free route to M1 [28,57,99]. SES at a high frequency is probably less effective than low-frequency SES for increasing corticospinal excitability but the reason is unclear. Perhaps SES at high
frequencies (e.g., 100 Hz) causes a saturation effect. Finally, it is also unclear if a given SES protocol would have to activate both muscle and cutaneous afferents for the most efficacious SES.

Table 2.1: Effects of somatosensory stimulation on motor performance and cortical measurements

<table>
<thead>
<tr>
<th>Participant</th>
<th>Year</th>
<th>Condition</th>
<th>Age (y)</th>
<th>Site of somatosensory stimulation</th>
<th>Muscle</th>
<th>Change in performance, %</th>
<th>Change in MEP size, %</th>
<th>Change in SICI, %</th>
<th>Change in ICF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conforto</td>
<td>2002</td>
<td>Stroke</td>
<td>65</td>
<td>Median</td>
<td>n/a</td>
<td>4.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDonnel*</td>
<td>2006</td>
<td>Healthy</td>
<td>39</td>
<td>APB + FDI</td>
<td>FDI</td>
<td>16</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sawaki</td>
<td>2006</td>
<td>Stroke</td>
<td>66.7</td>
<td>Ulnar + median + radial</td>
<td>n/a</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sawaki</td>
<td>2006</td>
<td>Healthy</td>
<td>32</td>
<td>Ulnar + median + radial</td>
<td>n/a</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu</td>
<td>2006</td>
<td>Stroke</td>
<td>64.5</td>
<td>Ulnar + median + radial</td>
<td>n/a</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celnik</td>
<td>2007</td>
<td>Stroke</td>
<td>55.2</td>
<td>Ulnar + median</td>
<td>FDI</td>
<td>7.2</td>
<td>-2.9</td>
<td>-37.9</td>
<td>36.1</td>
</tr>
<tr>
<td>Conforto</td>
<td>2007</td>
<td>Stroke</td>
<td>39.9</td>
<td>Median</td>
<td>n/a</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conforto</td>
<td>2007</td>
<td>Stroke</td>
<td>39.9</td>
<td>Median</td>
<td>n/a</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koesler</td>
<td>2009</td>
<td>Stroke</td>
<td>67</td>
<td>Median</td>
<td>n/a</td>
<td>26.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conforto</td>
<td>2010</td>
<td>Stroke</td>
<td>59.3</td>
<td>Median</td>
<td>APB</td>
<td>3.6</td>
<td>0.5</td>
<td>0.325</td>
<td>0.38</td>
</tr>
<tr>
<td>Conforto</td>
<td>2010</td>
<td>Stroke</td>
<td>64.2</td>
<td>Median</td>
<td>APB</td>
<td>3.4</td>
<td>-0.18</td>
<td>2.25</td>
<td>-0.31</td>
</tr>
<tr>
<td>Meunier*</td>
<td>2012</td>
<td>Dystonia</td>
<td>51.3</td>
<td>Median</td>
<td>FPB</td>
<td>27.8</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meunier*</td>
<td>2012</td>
<td>Healthy</td>
<td>46.3</td>
<td>Median</td>
<td>FPB</td>
<td>36.2</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorinola</td>
<td>2012</td>
<td>Healthy</td>
<td>27.1</td>
<td>Ulnar + median + radial</td>
<td>n/a</td>
<td>12.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*, study used somatosensory stimulation in the form of paired associative stimulation. APB: abductor pollicis brevis; FDI: first dorsal interosseus.
Figure 2.2. Neuroanatomical and conceptual models of the direct and crossed effects of somatosensory electrical stimulation (SES) on corticospinal excitability and motor output.

Panel A. Neuroanatomically established but simplified paths involved in the direct effects of median nerve SES (lightening sign) on corticospinal excitability in humans. The afferent stimulus ascends as it crosses at the medulla and reaches the receptive fields in areas 2, 1, 3a, and 3b forming the primary somatosensory cortex (S1) contralateral to the site of SES. Cutaneous inputs reach areas 1 and 3b and proprioceptive inputs reach areas 2 and 3a. SES also activates the secondary somatosensory cortex (S2, areas 40 and 43). In addition to the direct inputs, areas 2 and 3b receive excitatory inputs from S2. Direct S1-M1 connections via areas 1 and 2 and between S2 and M1 mildly activate M1. The present review identified specific SES...
parameters such as frequency (< 10 Hz) duration (> 20 minutes), and intensity (at or below motor threshold) that can increase corticospinal excitability in a median-nerve innervated muscle. Panels A and B do not show that SES also activate subcortical (nucleus cuneatus, ventral posterolateral nucleus of the rostral thalamus, cerebellum) and cortical structures (premotor area, supplementary motor area, areas 5 and 7 in the dorsal parietal cortex). There are insufficient and inclusive data whether spinal circuits contribute to these effects. In each panel, thicker lines represent a greater effect. The filled small circles symbolize the location of the stimulating electrodes over the median nerve.

**Panel B.** When SES is combined with motor practice (MP), S1 and S2 activation occurs as described in Panel A but activation of the contralateral M1 is greater (darker). SES with the parameters specified in Panel A, does not interfere with MP and M1 activation and corticospinal output and motor performance can increase, as quantified in Figure 2.1. Note that the bottom arrow from M1, i.e., improvement in motor performance is of the same thickness because currently there are no data suggesting a greater improvement in motor performance when motor practice is done with or without SES.

**Panel C.** Conceptual model based on known neuroanatomical paths of how SES could augment the effects of cross-education. SES and motor practice on one side strongly activates contralateral M1, S1, and S2. There is evidence that prolonged MP reduces interhemispheric inhibition (circle ended lines between M1s), i.e., the cross-education induced interhemispheric plasticity. Although the S1-S1 connections are inhibitory between areas 1 and 3b, connections between areas 2 are strongly excitatory. S2 is bilaterally activated and there are known excitatory connections from S2 to areas 2 and 3b and to M1. The net balance is an excitatory effect on M1 ipsilateral to SES. In combination with the diminished interhemispheric inhibition, SES could conceptually augment the cross-education effect. See text for more details. The model omits the known ipsilateral excitatory inputs to S2 on the side of SES and also does not show known cross-segmental excitatory effects produced by SES, which could play a role in SES’s effects to augment cross-education. Dashed lines represent the hypothetical crossed effects of corticospinal excitability and motor performance. See the text for details and references and Panel A for additional explanation of the used symbols.

**Panel D.** A second conceptual model based on known neuroanatomical paths how SES could augment the effects of cross-education. The left, non-involved hand performs motor practice and the right, involved hand concurrently receives SES. As in Panel A, SES primes S1-M1 connectivity. This model includes associated activity in the “resting” hand that occurs during unilateral motor tasks especially when the task is complex and requires a strong effort. Thus, the left-ipsilateral M1 becomes mildly active. The SES targeting the involved, right hand would therefore act on an M1 pre-activated by the associated activity. This interaction between SES and motor activity in the ipsilateral M1 would augment cross-education compared with unilateral practice without SES. Excitatory paths projecting to S1 from S2 via area 2 and from S1 to M1 on the ipsilateral side would facilitate the sensory element of the coupling between M1 and S1 on this side. We speculate that this paradigm would be especially suitable for orthopedic patients in whom, unlike in stroke patients, the injury would affect interhemispheric balance less. Dashed lines represent the hypothetical crossed effects of corticospinal excitability and motor performance. See the text for details and references and Panel A for additional explanation of the used symbols. In Panels C and D, the right hand does the motor practice because interlimb transfer is greater from right to left in right-hand dominant subjects.
SES could increase corticospinal excitability either through the individual or a combined effects of disinhibition, a GABA-ergic mechanism [125] and through long-term potentiation, a glutamergic mechanism. The data seem to suggest this latter mechanism being perhaps more tenable. When single afferent stimuli of SES targeting the median nerve are paired with TMS at an appropriate latency so that the two forms of stimuli bring about synchronized events in M1, there is a rapid and long-lasting rise in corticospinal excitability [48,94]. The afferent pulses, through the somatotopic connections between S1 and M1, pre-activate the motocortical cells. The TMS pulse thus acts on a population of disinhibited motocortical cells and the coupling increases corticospinal excitability. This conclusion is consistent with the pharmacological data, suggesting the action of a central GABAergic mechanism because the GABA-agonist lorazepam blocked the SES-induced increase in corticospinal excitability [58]. The 10 Hz frequency could be viewed as a threshold because, as discussed in the next section, all of the SES studies that showed improvements in motor function used 10 Hz (Table 2.1) and most studies also showed increases in corticospinal excitability at 10 Hz (Figure 2.1). Taken as a whole, this suggests that the 10-30 Hz threshold represents perhaps an optimal zone above which SES invokes a mechanism similar to long-term depression and below which it invokes a mechanism similar to long-term potentiation [125,126]. Figure 2.2A-B illustrate these mechanisms. We must note that the above conclusion seems to conflict with animal models but is in agreement with a previous survey’s conclusion [34]. Animal models tend to show a strengthening of synaptic connections after high frequency stimulation of cortical neurons through long-term potentiation, whereas here we provide evidence for frequent increases in corticospinal excitability after SES with frequencies as low as 10 Hz (Table 2.2 and Table S1 online supplement) (cf. [34]). However, it is uncertain how peripheral stimulation at 10 Hz is transformed into frequency modulation of cortical neurons.

Whether other mechanisms observed in animal preparations would also operate in the human studies reviewed herein remains speculative [126,127]. For example, there is no direct evidence for an unmasking of latent horizontal connections, activation of silent synapses, a modulation of activity-dependent synaptic plasticity, or for generalized changes in the excitability of postsynaptic neurons to occur after SES. An unmasking of existing but silent synaptic connections could mediate the rapid increases in motor cortical excitability following SES at an above motor-threshold intensity [58]. However, several studies reported increases in excitability after stimulation at below-motor threshold intensities (Table 2.2, Table S1 online supplement). While an up-regulation of postsynaptic AMPA receptors, an increase in the release of the excitatory neurotransmitter glutamate, and a reduction in GABAergic inhibition all could mediate the increase in excitability, the present review found no evidence for statistically significant changes in SICI, ICF, and other TMS indices that directly measure motor cortical excitability.

2.3 DIRECT EFFECTS OF SES CAN IMPROVE MOTOR PERFORMANCE

Table 2.1 shows the main characteristics of 10 studies that quantified changes in motor performance following SES in 68 stroke and dystonia patients 58 and 16 healthy adults [17,24,101,102,107,108,123,128-130]. Motor performance in this context refers to the
execution of skillful movements in the form of thumb abduction [107], (modified) Jebsen-Taylor-Hand-Function-Task [24,101,102,123,130], index finger tapping [128], and pinch strength [17]. Targeting up to three peripheral nerves innervating the hand, SES duration was 120 minutes in all but two studies, frequency ranged narrowly between 0.2 to 10 Hz, delivered in 10 Hz trains consisting of five, 1-ms-long pulses, and intensity ranged from below perceptual threshold [123] to three times perceptual threshold, producing “small motor responses” [24]. Although the SES parameters were remarkably uniform across these studies, improvements in hand motor performance varied widely (range 3 to 27%, mean 13 ±9%, p < 0.05, effect size: 1.3), possibly due to differences between patients’ clinical state, age, and gender. Improvements in hand function occurred immediately after SES and were still present 30 days after treatment with motor practice combined with SES [123]. Stimulation of one and up to three peripheral nerves at the same time improved motor performance similarly (14% vs. 16%). PAS (interstimulus interval 25 ms) improved motor performance 27% (±10, p < 0.05, effect size: 1.8) when it was delivered at 0.4 Hz at an intensity around motor threshold for a duration of 33 minutes in 17 dystonia patients and 46 healthy participants [108,129].

Prior research has suggested that SES delivered in trains vs. in a continuous form may be more effective for improving motor function because trains temporally more closely resemble the pattern of volleys discharged by motoneurons during natural activities such as cycling and walking [18,57]. The available data do not bear out this prediction because SES delivered in a continuous form (single study using PAS, mean 36%) seem to improve motor function to a greater extent than SES delivered in trains (mean 12%). Recent data in spinal cord injured patients (in combination with intense motor rehabilitation) and rodents receiving epidural stimulation at 40 Hz in a continuous stream for several weeks [131,132] complement the data in Table 2.1. Although it was suggested that SES is most effective when applied concurrently with motor practice [57,133], improvements in motor practice were 16% (p < 0.05; effect size: 1.3; range: 0.3 to 3.1) when SES was given alone or asynchronously [17,24,107,123,128,130] vs. only 7% when given in a combination [102]. A systematic manipulation of the timing of SES relative to motor practice showed increases in motor performance only when SES was combined with motor practice and not when SES preceded or followed motor practice [102], consistent with the data obtained in spinal cord patients [132]. However, under other conditions preconditioning with SES increased corticospinal excitability and improved the effects of motor practice [129]. Lower (0.83 x perceptual threshold) vs. higher intensity (2.1 x perceptual threshold) SES was more effective in improving hand motor function in stroke patients [101]. Statistically there were no additional benefits to patients receiving SES over multiple sessions vs. just one session because motor function improved 14% after one session and improved 28% more after 11 additional sessions with somewhat unique stimulation parameters (120 minutes, 10 Hz in trains with 5, 1-ms-long pulses below and twice perceptual threshold) [101].

The stimulation parameters that produced the larger and most reliable increases in corticospinal excitability (frequency ≤10 Hz, duration of about 120 min, intensity at or below motor threshold) grossly overlapped with those reviewed in the previous section for the analysis of excitability effects. However, of the 10 studies included in Table
2.1, only four measured MEP size, which increased over a broad range between -3 to 70%. However, the motor improvements did not correlate with changes in corticospinal excitability. Curiously, as reviewed in a previous section, SES and PAS inconsistently affected SICI (range +0.3 to -37.9%, Table 2.1) [48,58,95,97,102,108,123] and ICF. Overall, there are little and highly inconsistent data on the effects of systematically manipulating the dose of SES in relation to timing, duration, frequency, and intensity and how such changes would affect motor performance.

The mechanism of how SES improves motor performance remains unknown. Considering a lack of consistent evidence for correlated changes in motor performance, cortical, and corticospinal excitability we can only speculate how the beneficial effects of SES on motor performance might emanate. In those cases when motor improvements outlast the treatment duration by 2-3 hours, post-synaptic potentiation is an unlikely mechanism. The candidate mechanism probably also does not include active motor learning. One possibility is that prolonged SES modifies the gain of the afferent input and efferent output. In a somatotopically-organized manner, SES could augment neuronal excitability and produce use-dependent plasticity via long-term potentiation, which would subsequently allow the voluntary command to more effectively activate the target muscles. Perhaps the process could involve SES to cause an unmasking of synapses that were inactive before the treatment [102,107,108,126,127,134]. Although the data in Table 2.1 provide insufficient clues, still, most likely long-term potentiation is a key mechanism that could increase the active number of motoneurons and intracortical excitability. We suspect that SES modulates excitability through the afferent input and enables cortical and corticospinal cells that were not previously activated by the volitional drive, to become activated, resulting in greater and more forceful activation of motor units within a synergistic motoneuron pool. However, we do not know if motor practice and SES would each have to induce effects resembling long-term potentiation and if these individual effects would sum or such summation is actually not necessary for motor performance to improve [129].

2.4 CROSSED EFFECTS OF SES ON EXCITABILITY AND INTERLIMB TRANSFER

2.4.1 Background

This section reviews the crossed effects of SES on neural excitability and examines the hypothesis that unilateral motor practice in a certain combination with SES could augment interlimb transfer of muscle strength and motor skills in patients with unilateral motor impairments. Unilateral motor practice can cause rapid and lasting transfer of muscle force-generating capacity and skills to the non-exercised limb [37]. Although this effect is usually small, 7-10% in healthy human, there is growing evidence that unilateral motor practice with the non-impaired limb can produce clinically meaningful function-improving effects in the injury-free immobilized arm of healthy subjects [43,135-137], in patients with a wrist fracture [44], in individuals after anterior-cruciate ligament reconstruction [45,46], and in stroke patients [138,139]. If the idea is tenable that SES can augment interlimb transfer, it would add to the evolving repertoire of sensory augmentation of cross-education [38,41] and provide alternatives to conventional rehabilitation strategies such as constraint-induced movement therapy [42,140-145].
All studies used somatosensory stimulation in the form of paired associative stimulation (PAS). ISI: interstimulus interval; APB: abductor pollicis brevis; TA: tibialis anterior; IHI: interhemispheric inhibition; Ipsi: ipsilateral.

**Table 2.2: Crossed effects of somatosensory stimulation on neuronal excitability**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Year</th>
<th>Condition</th>
<th>Age (y)</th>
<th>Site of somatosensory stimulation</th>
<th>Muscle</th>
<th>ISI (ms)</th>
<th>Change in MEP size on stimulated site (%)</th>
<th>Change in MEP size on non-stimulated site (%)</th>
<th>Change in IHI (%)</th>
<th>Change in SICI (%)</th>
<th>Change in ICF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stefan</td>
<td>2000</td>
<td>Healthy</td>
<td>26</td>
<td>Median</td>
<td>APB</td>
<td>25</td>
<td>73</td>
<td>-15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jayaram</td>
<td>2008</td>
<td>Stroke</td>
<td>55</td>
<td>TA</td>
<td>TA</td>
<td>25</td>
<td>-16</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conde</td>
<td>2013</td>
<td>Healthy</td>
<td>25</td>
<td>Median</td>
<td>APB</td>
<td>45 (ipsiPAS)</td>
<td>-26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conde</td>
<td>2013</td>
<td>Healthy</td>
<td>25</td>
<td>Median</td>
<td>APB</td>
<td>60 (ipsiPAS)</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.4.2 Ipsilateral brain activation by SES

EEG, fMRI, MEG, PET, and TMS studies revealed that SES activates brain areas other than those involved in the direct effects. Prolonged SES at or below motor threshold produced bilateral activation in the pre- and postcentral and medial frontal gyri with particular consistency of S2 and supplementary motor area [62,105,121,146-154]. fMRI and EEG studies consistently showed that unilateral SES, as expected, strongly activated the contralateral S1 but activation of the ipsilateral S1 was more complex [111,113-115]. Of the four cytoarchitectonic subdivisions (areas 3a, 3b, 1 and 2), area 2 in the posterior part of the ipsilateral S1 showed excitation in primates [155] and in humans the activation of areas 2 and 5 was associated with a positive blood-oxygen-level-dependent response [152]. In contrast, areas 1 and 3b exhibited inhibition in alert monkeys [114] and were associated with a negative blood-oxygen-level-dependent response in humans [111,156]. The inhibition was SES intensity-dependent in areas 1 and 3b and the perceptual threshold in the other hand co-varied with SES intensity, suggesting that a functionally effective inhibition occurred [111,112] which can be reversed by peripheral anesthesia and cooling [157,158].

Inhibition of the ipsilateral S1 occurs most likely via interhemispheric paths. Areas 1, 2, and 3b have direct and perhaps also indirect transcallosal connections [155,159]. Lesions of the contralateral S1 abolished ipsilateral S1 potentials, confirming the transcallosal paths [155,160]. Cooling of area 3 in the ipsilateral S1, in contrast, enhanced neuronal activity and expanded the receptive fields in the homologous area in the monkey contralateral S1 [157]. A conditioning-test pulse paradigm of the left and right median nerve in healthy humans resulted in significant changes in N20 but not in N20/P25, N30, P40, and N60 in the ipsilateral (left) S1, providing further evidence for interhemispheric inhibitory interactions between left and right S1 [115]. However, the data are not entirely consistent because area 2, which has the densest callosal connections in primates [159] and in humans [152], is excitatory, whereas areas 3b and 1 have only few connections and are inhibitory [155]. All in all, it seems that transcallosal inhibition mediates the ipsilateral S1 deactivation during unilateral SES.

It is especially well documented that unilateral SES bilaterally activates S2 most likely due to interhemispheric information transfer through the posterior body of the corpus callosum with a latency of around 15 ms [155,159,161-166]. The possibility was also raised for group Ia, Ib, and II afferents to act via slow conducting ipsilateral thalamic projections to S2 [61,62,64,105,163,167,168]. Intra-cortical recordings as part of the stereotactic presurgical EEG assessment of patients with temporal lobe epilepsy confirmed these two paths to bilaterally activate S2 [163]. In addition, even after callosotomy, there was bilateral activity in S2 in response to unilateral stimulation [169].

2.4.3 Crossed effects of SES on motor cortical excitability

A handful of studies examined the crossed effects of SES on motor cortical, corticospinal, and spinal excitability (Table 2.2). Because of limited data in hand muscles, we had to relax the inclusion criteria for this part of the review and include studies in the leg and also studies that used SES of short duration (< 20 min). There is some evidence in primates for S1-S1 interhemispheric plasticity because the contralateral hemisphere
senses the effects induced by peripheral denervation and these changes are immediately mirrored in the other hemisphere [157,170]. Using the Stefan protocol [48] (90 pairs of single electric pulse at 3x perceptual threshold followed 25 ms later by a TMS pulse, delivered at 0.05 Hz), PAS of a digital nerve (thumb, mostly cutaneous afferents) and median nerve (cutaneous, muscle, and mechanoreceptor afferents) increased MEP size similarly 73% (p < 0.05) in the stimulated abductor pollicis brevis and decreased 15% (p > 0.05) in the non-stimulated abductor pollicis brevis [48]. In contrast, using the Müller protocol [171] (225 pairs of single electric pulse at 3xPT followed 25 ms later by a TMS pulse, delivered at 0.25 Hz), MEP recruitment curved shifted about 10 and 15% (p < 0.05) upward in the stimulated and non-stimulated abductor pollicis brevis, respectively. These changes in recruitment curves on the two sides correlated \( R^2 = 0.56 \), suggesting a strong crossed effect of PAS [172]. There were no changes (p > 0.05) in SICI (43% pre, 51% post) and ICF (144% vs. 131%) in the non-stimulated M1 but interhemispheric inhibition (IHI) from the stimulated to the non-stimulated M1 decreased from 66% to 82% (greater values reflects less IHI) and these reductions in IHI tended to correlate \( R^2 = 0.38 \) (p = 0.075) with changes in MEP size in the non-stimulated M1 [172]. PAS in a specific form when the TMS pulse is delivered not to the contralateral but instead to the M1 ipsilateral to median nerve stimulation, increased (60 ms interstimulus interval) and decreased (45 ms interstimulus interval) corticospinal excitability in the ipsilateral abductor pollicis brevis [110]. At 45 ms interstimulus interval, the peripheral and cortical stimulus pair arrives about at the same time at iM1 but at 60 ms, the electrical pulse arrives 15 ms before the magnetic pulse [110]. Note that the SES intensity was above motor threshold [110]. Inhibitory PAS for four minutes (120 pairs, 0.5 Hz) of the quiescent paretic tibialis anterior of 10 chronic stroke patients and healthy controls decreased MEP size 16% (p < 0.05) in the stimulated and increased MEP size 28% (p < 0.05) in the non-stimulated TA measured in the swing phase of gait, with the effects persisting for about 15 minutes [173]. In summary, under specific experimental conditions, SES can upregulate corticospinal excitability in M1 ipsilateral to the side of stimulation.

There is some evidence for crossed effects acting at the spinal level. Brief cutaneous forearm and mixed median nerve stimulation mildly tended to facilitate the H reflex about 10% (p = 0.060) in the homologous muscle on the opposite side [174]. Single electric pulses at around motor threshold delivered to the mixed median and radial nerve on one side, respectively, increased or decreased reciprocal inhibition 9% or 17% on the opposite side in the flexor carpi radialis in 22 healthy young adults [175]. Stimulation of pure sensory nerves produced no effects on reciprocal inhibition recorded on the opposite side [175]. Using seven interstimulus intervals, conditioning stimuli applied to the ipsilateral or contralateral second digit inhibited F-wave amplitude and persistence at 50 to 100 ms but facilitated contralateral F-waves at 80 to 200 interstimulus intervals [176] even though F waves may not be as valid as other measures of spinal excitability. In one subject, in whom it was possible to evoke an H reflex in the abductor pollicis brevis, contralateral facilitation of the H reflex also occurred [176]. In contrast to interhemispheric plasticity in primates [157,170], peripheral nerve lesions on one side had well-characterized and similar but smaller, briefer effects on the contralateral non-lesioned structures through an unidentified signaling mechanism [177].
2.4.4 SES to increase the effectiveness of cross-education

Fig. 1 shows that due to the direct effects of median nerve stimulation at a frequency < 10 Hz at or below motor threshold-intensity for a duration > 20 minutes, SES can increase corticospinal excitability and improve motor performance. Next we examine the possibility that SES could augment motor performance in the impaired limb as a result of cross-education [37]. In the cross-education paradigm, opposite to constraint induced therapy [42], patients with neurological or orthopedic conditions exercise the non- or less involved limb and this practice, through interlimb effects, improve function in the homologous muscle of the impaired limb [43-46,135-139]. Because this transfer effect is usually small, 7-10%, efforts are underway to identify methods that can increase the effectiveness of cross-education [38,41]. We present two models to show how the hypothetical effect might work.

2.4.5 Neuroanatomical and conceptual models

Figure 2.2C illustrates the hypothesis that SES could augment the cross-education effect via the contralateral S1 – contralateral M1 – IHI – ipsilateral M1 path. In this first model patients perform motor practice with the non-involved right hand and concurrently receive SES to the right side with the involved, left hand at rest. Motor practice and SES increase contralateral S1 excitability, which in turn raise contralateral M1 excitability (Figure 2.1). The increase in contralateral M1 excitability would then reduce IHI through transcallosal disinhibition and increase ipsilateral M1 excitability (relevant for the opposite involved, left hand). Data in healthy subjects and stroke patients provide some support for this mechanism [172,173]. The resulting plasticity in the hemisphere that receives the transfer is most likely the result of convergent inputs in ipsilateral S1 and ipsilateral M1 and would be compatible with activity-dependent plasticity. Data illustrating that chronic motor practice reduces IHI and this reduction is associated with behavioral gains in the practiced movement further supports this model [178]. The bilateral S2 activation through the known excitatory inputs via area 2 to ipsilateral M1 could prime ipsilateral M1 to receive transfer. This hypothesis must consider, as detailed in the previous paragraph, a role for Ia inhibitory interneurons modulating inputs to the motoneuron at the segmental level. This model would be suitable for orthopedic, stroke, and dystonia patients and we estimate based on the data in Figure 2.1 and Table 2.1 that SES would add to the cross-education effect (7-10%) about 5%, totaling about 12-15%. Ongoing experiments will provide critical data to support or refute this hypothesis.

Figure 2.2D depicts the second model in which the right, non-involved hand performs motor practice and the left, involved hand concurrently receives SES. As in Panel 2A, SES primes S1-M1 connectivity. An added component in this model is the well-documented presence of associated activity in the “resting” hand. That is, during a unilateral motor task, especially when the task is complex and requires a strong effort, the right-ipsilateral M1 also becomes increasingly activated [174,179-184]. These excitatory ipsilateral effects can be so strong that the homologous muscle in the “resting” left hand also becomes mildly activated [182,185-188]. Relevant to patients above age 40, this activation tends to increase with age, starting at middle age [189-193]. The SES targeting the involved, left hand would therefore act on an M1 area pre-activated by the associated activity produced by the contraction of the muscle on the right side. This mechanism would exploit the
ipsilateral M1-S1 coupling created by the SES acting on the top of the associated activity. Excitatory paths projecting to S1 from S2 via area 2 on the ipsilateral side would facilitate the sensory element of the coupling between M1 and S1 on the ipsilateral side. We speculate that this paradigm would be especially suitable for orthopedic patients in whom, unlike in stroke patients, the injury would affect interhemispheric balance less. Although stroke rehabilitation aims to down-regulate the contralesional hyperexcitable M1, SES therapy does not consider this step as a prerequisite because it raises the excitability in M1 and between S1-M1 in the involved hemisphere and could, according to two PAS protocols actually raise excitability in the hyperexcitable M1 [172,173]. For fracture patients, SES applied to the involved side, acting on top of associated activity will have to remain below motor threshold to avoid muscle contraction that could negatively influence healing. Clearly, further studies are needed in healthy adults first to determine the feasibility and the exact mechanisms of how and if SES could indeed augment the effects of cross-education. Without data supporting these hypotheses, we do not detail further untested possibilities wherein SES is given asynchronously to the impaired, right hand first followed by motor practice of the non-impaired, left hand [102] or wherein SES is given after motor practice to the impaired, right hand with the hope to facilitate consolidation of motor memory traces.

2.5 SUMMARY AND RECOMMENDATIONS

There are crossed as well as direct effects of SES on motor cortical excitability and motor performance. We examined the hypothesis that prolonged (> 20 minutes) electric form of SES at or below motor threshold-intensity increases corticospinal excitability, motor cortical excitability, brain activation and correlated improvements in motor function in healthy individuals or in those who suffer from a motor dysfunction. With respect to the direct effects, SES was most effective in increasing corticospinal excitability and improving motor performance at ≤ 10 Hz and at intensities of three times perceptual threshold or at motor threshold, producing very small muscle contractions. In 27 studies, including 299 healthy and 75 stroke and dystonia patients, SES increased corticospinal excitability (41%) and brain activation but we found no evidence for SES to affect TMS-derived intracortical measures. SES also increased motor performance 16%.

The limited data show that SES does produce facilitatory crossed effects under certain conditions using frequencies ≤ 10 Hz. There is evidence from imaging studies for SES at 40 Hz to inhibit ipsilateral S1. SES consistently activates S2 bilaterally. Of the many possibilities, we proposed two models of how SES could augment the effects of cross-education, expanding the evolving repertoire of sensory augmentation of cross-education [38,41] and providing alternatives to constraint-induced movement therapy [42] which is not suitable for patients with a unilateral orthopedic injury [43-46,137].

There are many key questions to be answered concerning the direct and crossed effects of SES. There is a need to standardize SES parameters and to examine the effects of systematic variation of SES duration, frequency, and intensity on M1 excitability, S1 activation, and motor performance. There is also a need to examine if delivering SES
before or after motor practice would, respectively prime the motor system and help with the consolidation of motor memory. There is a need to vary the versatility of outcomes along the motor skill continuum (simple, complex). There is little information about SES whether it is more effective in improving motor performance when delivered to one vs. two or more peripheral nerves. There is a need to develop an evidence-based rational for choosing the appropriate SES parameters according to task constraints and patient characteristics. Would SES at intensities above the motor threshold actually interfere with the execution of motor skills? Finally, there is a need for carefully designed experiments that examine the proposed mechanisms mediating the crossed effects produced by SES. Addressing these questions would help neurologists, physical therapists, and other rehabilitation experts to decide how best supplement motor practice with SES.
REFERENCES


88. Mang CS, Clair JM, Collins DF. Neuromuscular electrical stimulation has a global effect on corticospinal excitability for leg muscles and a focused effect for hand muscles. Exp Brain Res. 2011;209: 355-363.


<table>
<thead>
<tr>
<th>Author</th>
<th>Duration (min)</th>
<th>Frequency (Hz)</th>
<th>Pulse-duration (ms)</th>
<th>Intensity (5 categories)</th>
<th>Outcomes</th>
<th>Outcomes</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%motor performance (Cohen’s d)</td>
<td>%SICI (Cohen’s d)</td>
<td>%ICF (Cohen’s d)</td>
</tr>
<tr>
<td><strong>'Direct' effects of right-hand SES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridding</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>Low-motor</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaelin-Lang</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>High-sensory</td>
<td>-0.27</td>
<td>27.5</td>
<td>67.8</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>3.5</td>
<td>1</td>
<td>Low-motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chipchase</td>
<td>30</td>
<td>10</td>
<td>0.1</td>
<td>Low-sensory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chipchase</td>
<td>30</td>
<td>100</td>
<td>0.1</td>
<td>Low-sensory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chipchase</td>
<td>30</td>
<td>10</td>
<td>0.1</td>
<td>High-sensory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chipchase</td>
<td>30</td>
<td>30</td>
<td>0.1</td>
<td>Low-motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chipchase</td>
<td>30</td>
<td>10</td>
<td>0.1</td>
<td>High-sensory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chipchase</td>
<td>30</td>
<td>10</td>
<td>0.1</td>
<td>Noxious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schabrun</td>
<td>30</td>
<td>30</td>
<td>0.1</td>
<td>Low-motor</td>
<td>91.2</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Schabrun</td>
<td>30</td>
<td>100</td>
<td>0.1</td>
<td>Low-sensory</td>
<td>-68.8</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Mang</td>
<td>40</td>
<td>100</td>
<td>1</td>
<td>Low-motor</td>
<td>56</td>
<td>(1.31)</td>
<td></td>
</tr>
<tr>
<td>Ridding</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>Low-motor</td>
<td>97.5</td>
<td>(6.1)</td>
<td>50</td>
</tr>
<tr>
<td>Charlton</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>Low-motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlton</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>Low-motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sawaki</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>Low-motor</td>
<td>23</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Sawaki</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>Low-motor</td>
<td>20</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Wu</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>High-sensory</td>
<td>24</td>
<td>(3.1)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>SES Type</td>
<td>n</td>
<td>Study Type</td>
<td>Effect</td>
<td>Standard Error</td>
<td>p-value</td>
<td>Effect</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------</td>
<td>----</td>
<td>------------</td>
<td>--------</td>
<td>----------------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>Celnik (2007)</td>
<td>Low-sensory</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>7.2</td>
<td>0.42</td>
<td>-37.9</td>
</tr>
<tr>
<td>Conforto (2007)</td>
<td>Subthreshold</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conforto (2007)</td>
<td>High-sensory</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koesler (2009)</td>
<td>High-sensory</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>26.8</td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>Conforto (2010)</td>
<td>Subthreshold</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>3.6</td>
<td>0.02</td>
<td>0.325</td>
</tr>
<tr>
<td>Conforto (2010)</td>
<td>High-sensory</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>3.4</td>
<td>0.12</td>
<td>2.25</td>
</tr>
<tr>
<td>Conforto (2002)</td>
<td>Low-sensory</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>4.8</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Sorinola (2012)</td>
<td>Low-motor</td>
<td>120</td>
<td>10</td>
<td>1</td>
<td>12.5</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td><strong>'Crossed' effects of right-hand SES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manganotti (1997)</td>
<td>Low-motor</td>
<td>30</td>
<td>0.05</td>
<td></td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stefan (2000)</td>
<td>High-sensory</td>
<td>30</td>
<td>0.05</td>
<td></td>
<td>-15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hortobágyi (2003)</td>
<td>High-sensory</td>
<td>0.083</td>
<td>20</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jayaram (2008)</td>
<td>Low-motor</td>
<td>4</td>
<td>0.5</td>
<td></td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shin (2011)</td>
<td>High-sensory</td>
<td>1</td>
<td>0.25</td>
<td></td>
<td>-21.3</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>'Direct' effects of right-hand PAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stefan (2000)</td>
<td>High-sensory</td>
<td>30</td>
<td>0.05</td>
<td></td>
<td>-18</td>
<td>0.99</td>
<td>52</td>
</tr>
<tr>
<td>Stefan (2002)</td>
<td>High-sensory</td>
<td>30</td>
<td>0.05</td>
<td></td>
<td>-17</td>
<td>1.3</td>
<td>41.3</td>
</tr>
<tr>
<td>Castel-Lancanal (2007)</td>
<td>Low-motor</td>
<td>30</td>
<td>0.1</td>
<td></td>
<td>-4.7</td>
<td>0.73</td>
<td>0.11</td>
</tr>
<tr>
<td>Russman (2009)</td>
<td>High-sensory</td>
<td>20</td>
<td>0.2</td>
<td></td>
<td>-14.6</td>
<td>1.33</td>
<td>72.5</td>
</tr>
<tr>
<td>McKay (2002a)</td>
<td>Low-motor</td>
<td>45</td>
<td>10</td>
<td>1</td>
<td>-30.7</td>
<td>0.97</td>
<td>50</td>
</tr>
<tr>
<td>Pitcher</td>
<td>Low-motor</td>
<td>30</td>
<td>3</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Duration</td>
<td>Salience</td>
<td>MEU</td>
<td>Sensory</td>
<td>Motor</td>
<td>OEB</td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>----------</td>
<td>----------</td>
<td>-------</td>
<td>----------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>(2003) Pitcher</td>
<td>30</td>
<td>30</td>
<td>0.1</td>
<td>Low-motor</td>
<td>(0.5)</td>
<td>158.4</td>
<td>(0.59)</td>
</tr>
<tr>
<td>(2001) Ridding</td>
<td>30</td>
<td>10</td>
<td>1</td>
<td>Low-motor</td>
<td>-19</td>
<td>115.1</td>
<td>(1.31)</td>
</tr>
<tr>
<td>(2012) Meunier</td>
<td>20</td>
<td>0.2</td>
<td></td>
<td>High-sensory</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2012) Meunier</td>
<td>20</td>
<td>0.2</td>
<td></td>
<td>High-sensory</td>
<td>70</td>
<td>(4.4)</td>
<td></td>
</tr>
<tr>
<td>(2006) McDonnell</td>
<td>60</td>
<td>0.67</td>
<td></td>
<td>Low-motor</td>
<td>36</td>
<td>(1.79)</td>
<td></td>
</tr>
</tbody>
</table>