

1 **Determining the potential sites of neural adaptation to cross-education: Implications for**  
2 **the cross-education of muscle strength.**

3

4 Ashlyn K Frazer<sup>1</sup>, Alan J Pearce<sup>2</sup>, Glyn Howatson<sup>3,4</sup>, Kevin Thomas<sup>3</sup>, Stuart Goodall<sup>3</sup> and  
5 Dawson J Kidgell<sup>1</sup>

6

7 <sup>1</sup>Department of Physiotherapy, School of Primary Health Care, Faculty of Medicine, Nursing  
8 and Health Sciences, Monash University, Melbourne, Australia.

9 <sup>2</sup>Discipline of Exercise Science, School of Allied Health, La Trobe University, Melbourne,  
10 Australia.

11 <sup>3</sup>Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle-upon-  
12 Tyne, UK.

13 <sup>4</sup>Water Research Group, School of Biological Sciences, North West University,  
14 Potchefstroom, South Africa.

15

16 **Address for Corresponding author:**

17 Dr Ashlyn K Frazer, PhD

18 Department of Physiotherapy, School of Primary Health Care, Faculty of Medicine, Nursing  
19 and Health Science, Monash University, PO Box 527 Frankston, Victoria, Australia, 3199.

20 Email: ash.frazer@monash.edu

21

## 22 **Abstract**

23           Cross-education describes the strength gain in the opposite, untrained limb following a  
24 unilateral strength training program. Since its discovery in 1894, several studies now confirm  
25 the existence of cross-education in contexts that involve voluntary dynamic contractions,  
26 eccentric contraction, electrical stimulation, whole-body vibration and, more recently,  
27 following mirror feedback training. Although many aspects of cross-education have been  
28 established, the mediating neural mechanisms remain unclear. Overall, the findings of this  
29 review show that the neural adaptations to cross-education of muscle strength most likely  
30 represent a continuum of change within the central nervous system that involves both structural  
31 and functional changes within cortical motor and non-motor regions. Such changes are likely  
32 to be the result of more subtle changes along the entire neuroaxis which include, increased  
33 corticospinal excitability, reduced cortical inhibition, reduced interhemispheric inhibition,  
34 changes in voluntary activation and new regions of cortical activation. However, there is a need  
35 to widen the breadth of research by employing several neurophysiological techniques (together)  
36 to better understand the potential mechanisms mediating cross-education. This fundamental  
37 step is required in order to better prescribe targeted and effective guidelines for the clinical  
38 practice of cross-education. There is a need to determine whether similar cortical responses  
39 also occur in clinical populations where, perhaps, the benefits of cross-education could be best  
40 observed.

41

42 **Key words:** Connectivity, Cross-education, Mirror neurons, Excitability, Inhibition, Twitch  
43 force.

44

45

46 **List of Abbreviations**

47 **1-RM:** one-repetition maximum

48 **BOLD:** blood oxygenation level dependant

49 **FCR:** flexor carpi radialis

50 **fMRI:** functional magnetic resonance imaging

51 **FDI:** First Dorsal Interosseous

52 **GABA:**  $\gamma$ -Aminobutyric acid

53 **IHI:** interhemispheric inhibition

54 **LICI:** long-interval intracortical inhibition

55 **MEPs:** motor-evoked potentials

56 **MNS:** mirror neuron system

57 **MRI:** magnetic resonance imaging

58 **MVC:** maximal voluntary isometric contraction

59 **M1:** primary motor cortex

60 **rTMS:** repetitive transcranial magnetic stimulation

61 **sEMG:** surface electromyography

62 **SICI:** short intracortical inhibition

63 **tDCS:** transcranial direct current stimulation

64 **TMS:** transcranial magnetic stimulation

65 **V<sub>TMS</sub>:** voluntary activation measured with TMS

66 **WBV:** whole-body vibration training

67

68

69

## 70 **Introduction**

71       There is compelling evidence to support the hypothesis that a change in habitual physical  
72 activity, such as strength training, can induce adaptations in the nervous system (Duchateau et  
73 al. 2006; Gabriel et al. 2006; Carroll et al. 2011). One common observation that underscores  
74 the complexities of neural adaptations following a period of strength training is cross-education.  
75 This phenomenon specifically refers to the increase in muscle strength in one limb following  
76 unilateral strength training of the opposite limb (Manca et al. 2017a). Since the original  
77 observation by Scripture et al. (1894), there are now many published reports that have  
78 confirmed that the cross-education of muscle strength is a real effect (Manca et al. 2017a);  
79 however, the neural mechanisms mediating cross-education are less clear (Ruddy and Carson  
80 2013). Over the last 30 years, several studies have used surface electromyography (sEMG)  
81 recordings (Cannon and Cafarelli 1987, 1992; Mason et al. 2017a), electrical stimulation of  
82 peripheral nerves (Dragert and Zehr 2011; Fimland et al. 2009; Lagerquist et al. 2006),  
83 transcranial magnetic stimulation (TMS) (Goodwill et al. 2012; Hortobágyi et al. 2011; Manca  
84 et al. 2016a; Mason et al. 2017a), voluntary activation measured with TMS ( $VA_{TMS}$ ) (Lee et al.  
85 2009) and functional magnetic resonance imaging (fMRI) (Farthing et al. 2007; Palmer et al.  
86 2013; Ruddy et al. 2017) to study the neural adaptations to cross-education. Unfortunately, the  
87 neural mechanisms associated with cross-education remain elusive. Reports in the literature  
88 are markedly different and range from no substantial change (Latella et al. 2012) to persistent  
89 bilateral increases in corticospinal excitability (Hendy et al. 2015), reductions in corticospinal  
90 inhibition (Coombs et al. 2016), and short-interval intracortical inhibition (Hortobágyi et al  
91 2011). The complexity is further magnified because emerging evidence suggests some  
92 structural changes occur in both motor and non-motor areas (Ruddy et al. 2017). Furthermore,  
93 recent work has suggested that other brain regions and systems, such as the mirror neuron  
94 system (MNS) (Zult et al. 2016) and functional and structural connectivity (Ruddy et al. 2017)

95 could be important neural adaptations to cross-education. Subsequently, the aim of this  
96 narrative review is to critically evaluate and elucidate some of the reported important neural  
97 mechanisms and adaptations that have been implicated in the cross-education of muscle  
98 strength, and the potential implications of this phenomenon to clinical populations. This will  
99 be achieved by exploring the idea that the neural adaptations to cross-education are due to  
100 structural and functional changes within cortical motor and non-motor regions and subtle  
101 changes along the entire neuroaxis. This will be addressed by critically appraising the literature  
102 where neuroimaging and electrophysiological techniques, such as fMRI, TMS, VA<sub>TMS</sub> and  
103 spinal cord reflex studies have been used to explore the potential sites of neural adaptations to  
104 cross-education. Secondly, interventions which have been utilised to enhance the cross-  
105 education effect are then considered including, the mirror neuron system, non-invasive brain  
106 stimulation techniques such as transcranial direct current stimulation (tDCS),  
107 electromyostimulation and vibration training. Lastly, the potential clinical implications of  
108 cross-education are considered.

### 109 **Evidence for cross-education of muscular strength**

110 Since the first documentation of cross-education (Scripture et al. 1894), there has been a  
111 widespread fascination among the scientific community about the phenomenon whereby  
112 strength training of one limb results in an increase in strength of the opposite, untrained limb  
113 (Carroll et al. 2006; Munn et al. 2004). This phenomenon has been summarised in a recent  
114 meta-analysis by Manca et al. (2017a) that revealed a pooled cross-education effect on muscle  
115 strength of 11.9%. Following a quantitative analysis of 31 studies which drew data from 785  
116 subjects, the authors found a 9.4% effect for the upper limb and 16.4% for the lower limb (see  
117 Table 1A-D). The pooled contralateral increase in strength was substantially greater than  
118 originally reported (a pooled 7.8% increase (3.8% for the upper limb and 10.4% for the lower  
119 limb) from 16 studies involving 449 subjects (Carroll et al. 2006)). Of particular interest,

120 Manca et al. (2017a) demonstrated that the cross-education effect was not restricted to a  
121 particular contraction type, but is applicable to the entire muscle action spectrum across both  
122 upper and lower limbs. Although the magnitude of cross-education does differ between  
123 contraction type (isometric 8.2%; concentric 11.3%; eccentric 17.7%; isotonic-dynamic  
124 training 15.9%), all modes significantly increase contralateral strength following unilateral  
125 strength training (Manca et al. 2017a). Based upon these findings, it is likely that cross-  
126 education could be applied in context-specific environments, such as during different phases  
127 of musculoskeletal rehabilitation, in an attempt to maximize the cross-education of muscular  
128 strength and to attenuate strength loss and muscle atrophy following injury.

129

### 130 **Upper and lower limb effects**

131 The net effect of unilateral strength training of the upper limb is a contralateral increase in  
132 strength of 9.4% (Manca et al. 2017a). Of the 13 studies (two studies were excluded due to  
133 high heterogeneity) included by Manca et al. (2017a), five studies examined the hand/wrist  
134 muscles (Cannon and Cafarelli 1987; Coombs et al. 2016; Farthing et al. 2005; Manca et al.  
135 2016a; Yue and Cole 1992), two examined the wrist muscles (Kidgell et al. 2015; Lee et al.  
136 2009b) and six examined the elbow flexor muscles (Farthing and Chilibeck 2003; Kidgell et  
137 al. 2011; Meyers 1966; Munn et al. 2005; Shaver 1970, 1975). Although the cross-education  
138 model evidently exists in the upper limb, it appears that the effect is greater for the lower-limb  
139 musculature with a 16.4% increase in contralateral strength reported (15 studies [one study  
140 excluded due to high heterogeneity]) (Manca et al. 2017a). Most of the studies that were  
141 included in this recent meta-analysis involved training the knee extensors (12 studies)  
142 (Abazović et al. 2015; Carolan and Cafarelli 1992; Coratella et al. 2015; Garfinkel and Cafarelli  
143 1992; Goodwill et al. 2012; Hortobágyi et al. 1996, Hortobágyi et al. 1999; Kannus et al. 1992;

144 Latella et al. 2012; Lepley and Palmieri-Smith 2014; Weir et al. 1995, Weir et al. 1997), whilst  
145 the remaining studies examined the ankle muscles (four studies) (Fimland et al. 2009;  
146 Lagerquist et al. 2006; Manca et al. 2015; Shima et al. 2002). Interestingly, the magnitude of  
147 strength transfer was considerably more variable in the upper limb with a heterogeneity of 26%  
148 compared to the lower limb of 9% (Manca et al. 2017a). Although both heterogeneity scores  
149 are on the lower end of the continuum, it appears that the responses following strength training  
150 of the lower limb are uniform across different muscles and contraction modes. This difference  
151 may reside in the capacity to voluntarily activate the muscle of the upper or lower limb. The  
152 level of neural drive (i.e., motor output) to a muscle, which is also known as ‘voluntary  
153 activation’, can be assessed with the twitch interpolation technique (Allen et al. 1998) and via  
154 TMS cortical voluntary activation (e.g., VA<sub>TMS</sub>) (Carroll et al. 2008). Incomplete voluntary  
155 activation is associated with a reduction in the ‘voluntary’ force generating capacity of the  
156 muscle due to reduced neural drive at or above the site of stimulation of the motor nerve. It has  
157 been suggested that the capacity to increase muscle strength in upper-limb muscles may be  
158 limited when compared to lower-limb muscles due to high pre-existing levels of voluntary  
159 activation (Lee et al. 2009a) when compared to the lower-limb muscles (Ross et al. 2007; Sidhu  
160 et al. 2009). However, at present, there are not enough high-quality studies that have measured  
161 voluntary activation to conclude any differences, despite the recent finding, for at least the  
162 trained-limb voluntary activation is improved in the upper limb following strength training  
163 (Nuzzo et al. 2017). Although the magnitude of cross-education appears to be different between  
164 the upper and lower-limb muscles, other factors, such as contraction type (i.e., isometric,  
165 concentric, eccentric and isotonic) and the novelty of the training task are likely to influence  
166 the magnitude of cross-education (Farthing et al. 2005; Manca et al. 2017a).

167

168 **Contraction type**

169 At present, the greater part of cross-education studies has focused on the use of  
170 isometric and concentric training (Carroll et al. 2006; Manca et al. 2017a; Munn et al. 2004).  
171 However, eccentric contractions are known to provide a powerful stimulus for strength  
172 increases in the exercised and non-exercised limbs (Hortobágyi et al. 1997). This is supported  
173 by the finding of Manca et al. (2017a) who reported that eccentric and dynamic training  
174 protocols (i.e., concentric and eccentric contractions) induced significantly greater contralateral  
175 gains in strength than isometric contractions (eccentric 17.7%, dynamic 15.9% vs isometric  
176 8.2%). However, the number of studies using eccentric and dynamic training protocols is  
177 considerably less than those using isometric and concentric training protocols (Manca et al.  
178 2017a). Irrespective of this, the available evidence clearly indicates that the contralateral  
179 increase in muscle strength is real. This effect is strongest when the training employed has been  
180 matched to the strength outcome, showing that training specificity is very important (Kidgell  
181 et al. 2015; Manca et al. 2017a).

182 In the clinical context, it would be desirable to utilise a cross-education model that is likely  
183 to impart the greatest amount of strength transfer, thus training and testing specificity must be  
184 considered. Because the cross-education literature suggests that the magnitude of transfer is  
185 contraction-mode specific, the true benefits of cross-education will depend on how effective  
186 this contraction-mode training is within clinical populations. For example, it would be  
187 beneficial to explore whether eccentric training also transfers the largest amount of strength in  
188 different clinical populations. Furthermore, understanding the clinical effects of cross-  
189 education is important because the ability to activate muscles and produce force is critical for  
190 a number of activities of daily living. For example, there is a good correlation that exists  
191 between muscle strength and several clinical outcomes such as, gait speed (Suzuki et al. 2002),  
192 decreased risk of falls (Spink et al. 2011), and better balance (Moreland et al. 2004); also,  
193 people with greater strength levels tend to live longer (Legrand et al. 2014). In this regard,



194 understanding the neurophysiological changes that occur in the corticospinal tract and within  
195 motor and non-motor regions following a cross-education intervention is important, as it will  
196 advance our understanding of the neural adaptations that accompany the cross-education of  
197 muscle strength.

198

### 199 **Importance of the corticospinal tract as a potential site for neural adaptation to cross-** 200 **education**

201 The spinal cord is under the control of a number of neurones that descend from the  
202 primary motor cortex (M1). The largest of these are the corticospinal neurones that have their  
203 origins in layer V of the cerebral cortex and extend to form the bulk of the corticospinal or  
204 pyramidal tract (Porter, 1985). Although corticospinal neurones are located within six cortical  
205 regions, the M1 has the largest concentration (Porter, 1985). Within the M1, these corticospinal  
206 neurones are functionally organised to project to motoneurones that control specific muscle  
207 groups (Porter, 1985; He et al. 1993). Corticospinal neurones that arise within the M1 descend  
208 through the internal capsule, brainstem, and medulla oblongata to continue to descend in the  
209 dorsolateral funiculi of the spinal cord (Alawieh et al. 2017).

210 As the corticospinal neurones leave the M1 and descend to the medulla, they are  
211 organised somatotopically. At the medullary spinal junction, approximately 85-90% of the  
212 corticospinal neurones cross the midline to form the motor pyramidal decussation (Alawieh et  
213 al. 2017), where they continue as the dorsolateral funiculi of the spinal cord and converge onto  
214 motoneurones within the ventral horn of the spinal cord that innervate limb muscles (Alawieh  
215 et al. 2017). Anatomical mapping studies reveal that the connectivity of the corticospinal tract  
216 suggests that the remaining uncrossed ipsilateral corticospinal tract fibres descend primarily in  
217 the dorsolateral lateral or ventral funiculi of the spinal cord (Alawieh et al. 2017).

218 The ipsilateral corticospinal tract projections could have important implications for the  
219 cross-education of muscle strength as there is emerging evidence that suggests a potential site  
220 for adaptation could reside within the ipsilateral M1 itself (Goodwill et al. 2012; Kidgell et al.  
221 2011; Lee et al. 2010; Mason et al. 2017a). A small proportion of corticospinal tract fibres do  
222 not crossover at the pyramidal decussation at the medulla; rather, they project to ipsilateral  
223 spinal motoneurons, where they could alter the excitability of ipsilateral pathways (Alawieh et  
224 al. 2017; Carson, 2005). In the clinical neurophysiology literature, it has been suggested that  
225 increased utilisation of the ipsilateral pathway may provide a viable method for re-establishing  
226 motor control of upper-limb muscles following lesions to the M1 (Alawieh et al. 2017).

227

## 228 **Techniques to investigate the functional properties of the brain**

229 The ability to examine the human central nervous system (CNS) has developed  
230 remarkably over the last 30 years. Imaging techniques such as fMRI and positron emission  
231 topography (PET) indirectly measure the changes in blood flow associated with neural activity  
232 while participants perform a particular motor task (Jenkins et al. 1994). For example, there is  
233 a relationship between isometric force production, pre-movement activity and actual  
234 movement execution that results in increased cortical activity in the M1, supplementary motor  
235 area (SMA) and the dorsal portion of the anterior cingulate cortex (Dettmers et al. 1995;  
236 Thickbroom et al. 1999; Farthing et al. 2007). Recently, neuroimaging techniques have been  
237 used to provide insight into the potential neural adaptations to cross-education (Farthing et al.  
238 2007, Palmer et al. 2013; Ruddy et al. 2017). Although these studies demonstrate changes in  
239 blood flow during movement preparation and execution, they do not provide any objective data  
240 concerning the excitatory and inhibitory synaptic events specific to the M1 during movement  
241 (Hallett 2007). TMS, a non-invasive neurostimulatory technique, can provide a solution to

242 some of these limitations as it allows the net excitatory and inhibitory synaptic activity within  
243 the M1 and corticospinal tract to be determined with excellent time resolution (Hallett 2007).  
244 There is now a growing body of evidence that shows that there are changes in the efficacy of  
245 neural transmission along the corticospinal tract following cross-education (Goodwill et al.  
246 2012; Kidgell et al. 2011; Lee et al. 2009; Mason et al. 2017a) and new regions of activation  
247 as assessed by fMRI (Farthing et al. 2007; Palmer et al. 2013; Ruddy et al. 2017).

248

### 249 **Structural and functional cortical activity and cross-education**

250 The cross-education of muscle strength has historically been associated with changes in  
251 the neural control of the untrained limb, namely, increased capacity to voluntarily activate the  
252 untrained muscle. This observation is based upon the change in strength of an untrained limb  
253 which occurs in the absence of muscle hypertrophy, although changes in the intrinsic properties  
254 of the untrained homologous muscle cannot be excluded (Hendy and Lamon 2017). Despite  
255 possible muscle effects, the consensus suggests that the cross-education effect, in part, is  
256 mediated by changes in the activity of neural circuits, but the site of such change (i.e., cortical  
257 or subcortical) remains unclear. It is not known whether bilateral corticospinal excitability and  
258 inhibition generated during unilateral motor training are the genesis for concurrent neural  
259 adaptations in both cerebral hemispheres (Hellebrandt 1951). Although studies have reported  
260 bilateral activation of the M1 during unilateral movements (Kobayashi et al. 2003; Ruddy et al.  
261 2016), to date, there are few studies that have reported bilateral cortical activity of the M1  
262 following cross-education of muscle strength (Frazer et al. 2017; Hendy and Kidgell 2014;  
263 Hendy et al. 2015; Mason et al. 2017a). An emerging approach that may add new knowledge  
264 regarding the neural adaptations underpinning the cross-education is the use of neuroimaging  
265 techniques. There are now several neuroimaging studies that show, that during unilateral

266 movements, several regions of activation within pre-motor areas outside of the M1 are involved.  
267 These recent findings suggest that there is a greater need to understand the structural and  
268 functional bases of cross-education (Farthing et al. 2007; Koeneke et al. 2004) and their causal  
269 effect in increasing muscle strength of the untrained limb.

270

## 271 **Neuro-imaging and cross-education**

272 Evidence suggests that the cerebral responses to cross-education are controlled centrally  
273 by communication between the cerebral hemispheres, via interhemispheric communication and  
274 bilateral cortical activity (Hortobágyi et al. 2011; Perez and Cohen 2009). There is a growing  
275 need to obtain detailed knowledge of the structural and functional connectivity patterns within  
276 the brain following cross-education training. In vivo neuroimaging, such as spatiotemporally  
277 resolved magnetic resonance imaging (MRI), alongside its functional variant, fMRI, is one of  
278 the pre-eminent tools that is capable of capturing the interaction between neural substrates and  
279 action in humans. fMRI is a non-invasive technique that detects changes in regional blood flow  
280 within cortical structures in response to a motor task and is quantified as a change in the blood  
281 oxygenation level dependant (BOLD) contrast or ratio of deoxygenated haemoglobin (Kelly  
282 and Garavan 2005). Changes in the BOLD response are representative of a change in the  
283 activation of neural circuits (Xiong et al. 2009), but the BOLD response is not a direct measure  
284 of synaptic activity or the presence action potential activity. Thus, any interpretation from  
285 BOLD changes should be made with caution as a number of biological process may be involved.  
286 For example, changes in activation could be accompanied by changes in synaptic activity  
287 within brain structures that are involved in movement (Palmer et al. 2013). Nevertheless, fMRI  
288 has been used to detect temporal correlations in spontaneous BOLD responses while subjects  
289 remain at rest. These BOLD responses reveal that multiple cortical brain regions are

290 functionally connected forming resting-state networks. Interestingly, the level of functional  
291 connectivity within resting-state networks suggests the existence of direct structural (i.e.,  
292 neuroanatomical) connections between functionally-linked brain regions (Cordes et al. 2001).  
293 Such structural and functional connectivity facilitates the ongoing inter-regional neuronal  
294 communication. Importantly, the structural integrity of white-matter tracts, which are structural  
295 neural pathways within the brain, facilitates the transmission of neural communication from  
296 one brain region to another (Greicius et al. 2009). Understanding changes in structural and  
297 functional connectivity following cross-education will add new knowledge regarding the  
298 potential sites and mechanism of strength development for the untrained limb.

### 299 ***Regions of cortical activation and their implications for cross-education***

300         There is experimental evidence that suggests regions outside, but functionally  
301 connected to the M1, may mediate the neural adaptations of cross-education (Farthing et al.  
302 2007; Ruddy et al. 2017; see Table 1). For example, during unilateral movements, there are  
303 larger increases in the BOLD response within the premotor cortex (Koenke et al. 2004),  
304 supplementary motor area (Grafton et al. 2002) and cingulate motor area (Kermadi 2000).  
305 Structural connectivity reveals that the dorsal premotor cortex, supplementary motor area and  
306 cingulate motor area have dense structural white-matter connections within the homologous  
307 zone in the opposite cerebral hemisphere (Ruddy et al. 2017). At a minimum, this suggests that  
308 a structural basis exists for cross-education and may be a specific neural strategy used by the  
309 nervous system for increasing the strength of an untrained limb. This line of inquiry is  
310 supported when assessing the functional importance of these structural connections. The  
311 supplementary motor area is a critical region for motor learning as it plays an important role in  
312 modulating the timing of force output (Haller et al. 2009) and is associated with cortical  
313 plasticity following motor learning (Grafton et al. 1995, 2002; Perez et al. 2007b). In addition,  
314 the supplementary motor area controls both the contralateral and ipsilateral limbs during

315 sequence motor learning (Brinkman and Kuypers 1973). Perez et al. (2007b) showed that when  
316 repetitive TMS (rTMS) was applied to the supplementary motor area, it abolished the cross-  
317 transfer of a sequenced motor-learning task to an untrained limb, but it had no effect on the  
318 performance gains of the trained limb. Recent evidence now confirms that the structural  
319 connectivity of bilateral supplementary motor areas is substantially greater than any other  
320 bilateral regions of the motor cortical network (e.g., M1; Ruddy et al. 2017). In support of this,  
321 Ruddy et al. (2017) showed that, following an acute bout of 300 ballistic wrist-flexion  
322 movements, motor performance of the untrained limb improved and was associated with an  
323 increase in functional connectivity between the right and left supplementary motor area. These  
324 observations show that unilateral motor-training engages interhemispheric pathways and that  
325 the level of structural connectivity (i.e., the connecting white-matter pathways) influences the  
326 magnitude of cross-education (Ruddy et al. 2017). Although this provides new evidence and a  
327 good rationale for other cortical structures to be involved in the cross-education of muscle  
328 strength, to date, there have been no long-term cross-education studies to show that there are  
329 persistent changes in connectivity between left and right supplementary motor areas.

330         The dorsal premotor region has strong bilateral connections to the prefrontal cortex,  
331 parietal cortex and striatum, and this may also serve as a pathway mediating cross-education  
332 of strength. In primates, stimulation of the premotor cortex leads to an observable twitch  
333 response, showing its contribution to motor output during movement (Dum and Strick 2005;  
334 He et al. 1995). Further, because the dorsal premotor cortex has direct projections to the spinal  
335 motoneurone pool and shared connections with the ipsilateral M1, it is a candidate structure  
336 that could modulate the output from the M1 following cross-education (He et al. 1993).  
337 Neuroimaging data support strong interhemispheric bilateral connections between the dorsal  
338 premotor cortices (Fling et al. 2011), and structural connectivity reveals that the anterior dorsal  
339 premotor area has connections to the prefrontal cortex, whilst the posterior regions have direct

340 projections to the M1 and spinal cord (Schubotz and von Cramon 2002). These structural and  
341 functional connections provide cortical loci that could mediate cross-education. However, a  
342 caveat to this interpretation is that there have been no cross-education studies that have  
343 examined the pattern of activation within the dorsal premotor cortex. Rather, most of the  
344 current understanding for this region is based upon the motor-learning literature (Hardwick et  
345 al. 2013). A significant drawback with imaging is that changes in the fMRI BOLD signal do  
346 not reveal any changes in the synaptic behaviour regarding these new regions of cortical  
347 connectivity.

348         A cortical network, not thoroughly explored, that could contribute to cross-education is  
349 the cingulate motor area. The cingulate motor area is active during unilateral limb movements  
350 but, importantly, the level of activation increases as a function of increased force output  
351 (Winterer et al. 2002). It is likely that chronic high-force unilateral training may result in  
352 persistent changes in connectivity of the cingulate motor area. This hypothesis is possible  
353 because of the strong connections between the cingulate motor area and the homologous region  
354 in the opposite cerebral hemisphere (Ruddy et al. 2017).

355

356

### 357 *Neuroimaging studies and cross-education*

358         The origins of structural and functional connectivity provide the opportunity to explore  
359 brain networks following cross-education; however, to date, there has only been one acute  
360 cross-education study (i.e., a single training bout) (Ruddy et al. 2017) and two long-term cross-  
361 education studies (six and four week training interventions) (Farthing et al. 2007; Palmer et al.  
362 2013) that have used neuroimaging to determine potential sites and patterns of cortical  
363 activation.

364 Using a ballistic training task for the left-wrist flexors, Ruddy et al. (2017)  
365 demonstrated that the increase in performance of the untrained limb was 83% of that observed  
366 for the trained limb, and that there was a significant increase in functional connectivity in the  
367 resting motor network between the right and left supplementary motor areas. Interestingly, the  
368 increase in functional connectivity was not associated with the individual level of cross-  
369 education. Intriguingly, fibre density in the neural tracts (white matter) connecting the bilateral  
370 supplementary motor areas was negatively correlated with cross-education. Although this was  
371 only an observation following an acute bout of unilateral motor training, the finding suggests  
372 that interhemispheric pathways and the structural integrity of the connecting white-matter  
373 pathways of the supplementary motor area play a crucial role in cross-education. Although this  
374 is an interesting finding, it remains unclear if repeated high-force voluntary contractions  
375 performed over 2-4 weeks lead to a similar effect in structural and functional connectivity.

376 Farthing et al. (2007) were the first to examine the training-related effects of cross-  
377 education on patterns of brain activation following a six-week unilateral strength-training  
378 intervention. Strength of the left untrained limb improved by 47% and there was a persistent  
379 increase in activation of the sensorimotor cortex and bilateral M1, which is consistent with the  
380 motor-learning literature (Grafton et al. 2002). The cross-education of strength was also  
381 accompanied by an increase in the pattern of activation within the temporal lobe and the right  
382 and left cerebellum (Farthing et al. 2007). Because there was an increase in activation of the  
383 M1, supplementary motor area and temporal region following cross-education, this finding  
384 supports the recent evidence from Ruddy et al. (2017) that there are structural and functional  
385 changes within cortical networks following unilateral motor practice.

386 Palmer et al. (2013) examined the effects of four-weeks of strength training of the lower  
387 limb on structural connectivity. Training consisted of six sets of six maximal voluntary  
388 contractions (MVCs) of the dominant-leg plantar flexors. MVC was measured pre and post for



389 the trained and untrained leg. Strength training increased plantar flexion strength by 30% in  
390 the untrained limb; however, this change was not accompanied by any structural brain changes  
391 which is in contrast to the findings of Farthing et al. (2007). Physiological interpretation of  
392 changes in regions of brain activation obtained from fMRI should be made with caution as  
393 there could be a range of other physiological processes that supplement changes in brain  
394 activation, such as neuronal activation from between and within brain regions that occur during  
395 movement. Therefore, there is a need to examine the muscle-specific pattern of cortical activity  
396 following upper- and lower-limb cross-education using multiple techniques.

397         In light of the above, given the recent emergence of neuroimaging data, it seems  
398 reasonable to suggest that the cross-education of strength is associated with patterns of brain  
399 activation because of repeated training. The finding of increased activation of the temporal  
400 region following cross-education has important implications for understanding the mechanisms  
401 of strength transfer (Farthing et al. 2007). For some time, cross-education has been considered  
402 a form of motor learning and there are several lines of evidence that the temporal region is  
403 important for memory recall (Martin et al. 1995). In theory, memory retrieval could be  
404 important for cross-education in regards to providing an internal representation of a movement  
405 previously acquired by the opposite limb (Obayashi 2004). This hypothesis supports earlier  
406 findings within the motor-learning literature where the temporal region has been implicated  
407 (Farthing et al. 2007). Increased activation within the right and left cerebellum also suggests  
408 that cross-education training may improve the timing and activation of agonists, antagonists  
409 and synergist muscle groups which improve the coordination of a movement task. There is  
410 good evidence that cross-education training improves patterns of muscle activation (Cannon  
411 and Cafarelli 1987; Carolan and Cafarelli 1992; Farthing et al. 2005; Fimland et al. 2009;  
412 Garfinkel and Cafarelli 1992; Mason et al. 2017a; Perez et al. 2007a) and such changes are  
413 likely a result of changes in activation of the cerebellum (Obayashi 2004).

414           Although new regions of activation have emerged as potential sites of adaptation  
415 following cross-education, fMRI is not able to determine the intracortical mechanisms  
416 underlying increased activation. For example, it remains unclear whether excitatory or  
417 inhibitory mechanisms underlie the changes in the BOLD responses (Logothetis 2003).  
418 Therefore, there is a need to combine neuroimaging techniques with electrophysiological  
419 techniques, such as single- and paired-pulse TMS and quantitative electroencephalography, to  
420 determine the spatial and temporal effects of cross-education.

421

### 422 **Neurophysiological mechanisms mediating cross-education**

423           A consistently reported neural adaptation to cross-education is bilateral cortical activity  
424 (Frazer et al. 2017; Hendy and Kidgell 2014; Lee et al. 2010) whereby, during unilateral  
425 strength training, there is concurrent activation in both cerebral hemispheres that are involved  
426 in motor output. The M1 ipsilateral to the training limb has been shown to play an important  
427 role in mediating the cross-education effect (Frazer et al. 2017; Hendy et al. 2015; Hortobágyi  
428 et al. 2011; Lee et al. 2010). Specifically, cross-education studies have reported increased  
429 corticospinal excitability (Kidgell et al. 2015), decreased corticospinal inhibition (Coombs et  
430 al. 2016; Hendy et al. 2015), reduced interhemispheric inhibition (IHI) (Hortobágyi et al. 2011;  
431 Zult et al. 2016) and increased  $VA_{TMS}$  (Lee et al. 2009b) in the M1 ipsilateral to the training  
432 limb.

433

### 434 **The use of TMS to examine the cortical responses to cross-education**

435           TMS is one of the most robust tools available to study the function of the M1 following  
436 a motor-training intervention. Briefly, TMS requires placing a wire coil over the M1 ‘hot spot’  
437 of the target representation of the trained muscle (Hallett 2007). When the magnetic coil is

438 discharged over the M1, it generates a brief ( $\leq 100 \mu\text{s}$ ) high-current pulse that passes painlessly  
439 through the skull (Hallett 2007; Rothwell et al. 2009). When the intensity of the TMS pulse is  
440 sufficiently large, it primarily activates cortico-cortical axons which provide excitatory inputs  
441 onto corticospinal output neurones, depolarising them trans-synaptically as I-waves, with some  
442 in close proximity to the axon hillock as D-waves (Di Lazzaro et al. 1999). The net result is the  
443 production of a series of descending volleys (action potentials) that travel along the  
444 corticospinal tract, synapsing at the appropriate lower-motoneurone pool within the spinal cord,  
445 eliciting a brief, relatively synchronous muscle response in the contralateral side of the body.  
446 The response is recorded using sEMG and is referred to as a motor-evoked potential (MEP)  
447 (Hallett 2007).

448         MEPs represent the balance between the net excitatory and inhibitory influences on the  
449 corticospinal tract as a whole, including those from cortical circuitry, the motoneurone pool,  
450 and spinal interneuronal relays (Hallett 2007; Kidgell et al. 2017). Therefore, it is difficult to  
451 ascertain the exact site(s) of adaptation with a single-pulse TMS protocol following a motor-  
452 training intervention; however, MEPs still provide several important physiological variables  
453 that represent the overall efficacy of neural transmission along the corticospinal tract (Rossini  
454 and Rossi 2007). The amplitude of the MEP reflects the integrity of the corticospinal tract, the  
455 excitability of the M1, and the efficiency of neural conduction along the peripheral motor  
456 pathway (Hallett 2007). Conversely, the corticospinal silent period, a period of electrical  
457 silence immediately following a MEP evoked in an active muscle, represents inhibition along  
458 the corticospinal tract (Wilson et al. 1993). The early portion (50-75 ms) is primarily caused  
459 by segmental mechanisms, such as Renshaw cell recurrent inhibition and activation of Ia  
460 interneurons by descending corticospinal volleys. The latter portion ( $>75$  ms) is caused by  
461 cortical gamma-aminobutyric acid (GABA), specifically GABA<sub>B</sub> contributions (Fuhr et al.  
462 1991). There are now several cross-education studies that have examined the MEP amplitude

463 and corticospinal silent period duration of the M1 ipsilateral to the trained limb (Coombs et al.  
464 2016; Goodwill et al. 2012; Hortobágyi et al. 2011; Kidgell et al. 2011, 2015; Latella et al.  
465 2012; Manca et al. 2016a; Mason et al. 2017a). However, the findings are mixed. For example,  
466 some studies have reported increased MEP amplitudes (Mason et al. 2017a; Hendy et al. 2015),  
467 whilst others have shown no change (Coombs et al. 2016; Latella et al. 2012); those that  
468 examined the corticospinal silent period have shown reductions (Coombs et al. 2016, Kidgell  
469 et al. 2015).

470         Although single-pulse TMS can provide useful information about the excitability of the  
471 corticospinal tract, paired-pulse TMS allows an objective assessment of the physiology of the  
472 intrinsic cortico-cortical connections within the M1 (Kujirai et al. 1993). Paired-pulse TMS  
473 that uses a sub-threshold conditioning stimulus (70-80% motor threshold), delivered 2-4 ms  
474 prior to a supra-threshold test-stimulus, results in a suppressed paired-pulse MEP compared to  
475 a baseline single-pulse MEP (Rothwell et al. 2009). This protocol allows the estimation of the  
476 excitability of GABA<sub>A</sub>-ergic circuits within the M1 by calculating the ratio between the  
477 conditioned and unconditioned MEPs, which is known as short-interval intracortical inhibition  
478 (SICI). SICI is synaptic in origin and mediated by the activation of low-threshold inhibitory  
479 circuits that have a presence of GABA<sub>A</sub> receptors from the sub-threshold conditioning stimulus  
480 (Kujirai et al. 1993). Paired-pulse TMS enables the measurement of synaptic efficacy of  
481 inhibitory neural networks detectable at the level of the M1 following cross-education  
482 (Goodwill et al. 2012). In fact, several cross-education studies have now shown that SICI is  
483 reduced within the M1 ipsilateral to the training limb (Goodwill et al. 2012; Kidgell et al. 2015).

484         In a similar manner, when a suprathreshold TMS pulse at an inter-stimulus interval  
485 (ISIs) of 50-200 ms is applied, MEPs are significantly reduced and are referred to as long-  
486 interval intracortical inhibition (LICI) and this is representative of a slow-phase inhibitory  
487 circuit (Valls-Solé et al. 1992). Similar to the corticospinal silent period, LICI is thought to

488 reflect GABA<sub>B</sub>-mediated cortical inhibition. To date, there has only been one study that has  
489 examined the effect of cross-education on LICI and it reported no changes in LICI in the  
490 ipsilateral M1 (Manca et al. 2016a).

491 Although TMS is an emerging technique that can be used to provide insight into the  
492 neural adaptations to cross-education, there are several limitations that should be considered  
493 when interpreting the literature. It must be recognised that the amplitude of MEPs are  
494 influenced by numerous factors along the brain-to-muscle pathway. For example, the  
495 excitability of the corticospinal and intracortical neurones that are activated by TMS and the  
496 efficacy of the synapses between these neurones can influence MEP amplitude (Mazzocchio et  
497 al. 1994; Ugawa et al. 1995). Further, the excitability of interneurones located between  
498 corticospinal neurones and  $\alpha$ -motoneurones, the efficacy of the corticospinal-motoneuronal  
499 synapses (Bunday and Perez, 2012; Taylor and Martin, 2009), and the excitability of the  
500 motoneurones themselves (Nielsen and Petersen, 1995; Di Lazzaro et al. 1998), all affect the  
501 amplitude of MEPs.

### 502 ***Ipsilateral MEP responses to cross-education***

503 There are now several studies that have reported that cross-education of muscle strength  
504 is accompanied by an increase in ipsilateral corticospinal excitability (i.e., MEPs) following  
505 dynamic, eccentric and concentric training, (Goodwill et al. 2012; Kidgell et al. 2011; Mason  
506 et al. 2017a), eccentric (Kidgell et al. 2015) and isometric strength-training (Hortobágyi et al.  
507 2011). However, similar to the TMS strength-training literature, this finding is not always  
508 consistent (Kidgell et al. 2017). For example, just as many studies have shown no change in  
509 ipsilateral corticospinal excitability (Coombs et al. 2016; Latella et al. 2012; Manca et al.  
510 2016a). These inconsistencies appear to be driven by the different TMS methods employed,

511 muscles trained, intensity of the training stimulus, and the mode of muscle contraction used  
512 during training.

513           Historically, the cross-education effect was thought to be confined to the contralateral  
514 homologous muscle; however, recent experimental data suggested that the effects exist beyond  
515 the contralateral agonist muscle (Mason et al. 2017a). Recently, we (Mason et al. 2017a)  
516 examined the spatial effects of cross-education on ipsilateral corticospinal excitability. Briefly,  
517 participants completed 3-weeks of high intensity (80% one repetition maximum [1-RM])  
518 elbow-flexion training and we recorded MEPs from agonist and synergist muscles by  
519 stimulating ipsilateral M1 prior to, and following, the training period. The MEPs of the  
520 untrained elbow-flexors increased but there were no changes in MEPs of the untrained  
521 synergistic wrist-flexors (Mason et al. 2017a), yet we showed increased strength in both the  
522 contralateral agonist and synergist. We also reported a similar finding for corticospinal silent  
523 period duration. These findings raise questions as to why there was not any increase in the MEP  
524 and any decrease in corticospinal silent period duration of the synergist muscle despite  
525 reporting an increase in strength. As alluded to earlier, it is likely the spatial effects of strength  
526 transfer could be mediated by other cortical structures, but functionally linked to the ipsilateral  
527 M1 that TMS is unable to detect. Overall, the ipsilateral MEP responses to cross-education are  
528 inconsistent across studies and confined to the contralateral homologous motor-cortical  
529 network. To this end, there is no clear evidence to support a role for increased corticospinal  
530 excitability of the M1 ipsilateral to the training limb as a mechanism that mediates the cross-  
531 education of strength (see Table 2).

### 532 ***Ipsilateral inhibitory responses to cross-education***

533           Unlike the MEP responses to cross-education, there is stronger evidence that shows an  
534 important neural adaptation to cross-education is a reduction in intracortical inhibition of the

535 ipsilateral M1 (Coombs et al. 2016; Goodwill et al. 2012; Hortobágyi et al. 2011; Kidgell et al.  
536 2015; Latella et al. 2012; Mason et al. 2017a). For example, work from our laboratory showed  
537 that there is a 12-18 ms reduction in the corticospinal silent period following both upper-  
538 (Coombs et al. 2016; Kidgell et al. 2015; Latella et al. 2012; Mason et al. 2017a) and lower-  
539 limb cross-education (Goodwill et al. 2012; Latella et al. 2012). There is also good evidence  
540 that shows SICI is reduced (Goodwill et al. 2012; Hendy et al. 2015; Kidgell et al. 2015),  
541 suggesting cross-education selectively reduces the synaptic efficacy of inhibitory networks  
542 within the ipsilateral M1 and corticospinal tract. Because the corticospinal silent period is  
543 modified by GABA<sub>B</sub>-mediated inhibition (Werhahn et al. 1995), it seems that cross-education  
544 specifically affects intracortical inhibitory neurones that collectively results in an improved  
545 ability to activate the spinal motoneurone pool, which could partly explain the increases in  
546 muscle strength.

547         The reduced corticospinal silent period and SICI show that the GABA-ergic inhibitory  
548 neural networks are important for maximal force generation and are associated with the cross-  
549 education of muscle strength (Christie and Kamen 2013; Coombs et al. 2016; Kidgell and  
550 Pearce 2010; Weier et al. 2012). This line of enquiry is supported by early theories of cross-  
551 education whereby reductions in IHI could play a pivotal role in the behavioural effects  
552 observed (Hellebrandt 1951; Hortobágyi et al. 2011). The reduction in corticospinal inhibition  
553 seems to be an important mechanism that mediates cross-education because several studies,  
554 that have used models of immobilization, have reported increased silent-period durations and  
555 reduced muscle-strength (Clark et al. 2008; Pearce et al. 2012); however, motor training seems  
556 to attenuate the prolongation of the corticospinal silent period (Clark et al. 2014).

557         The reduction in SICI following cross-education suggests that the excitability of short-  
558 latency intracortical inhibitory circuits are reduced, which serves to focus the excitatory drive  
559 onto corticospinal neurones within the ipsilateral M1 that produce the intended movement of

560 the agonist muscle (Reynolds and Ashby 1999; Ridding et al. 1995). Certainly, evidence is  
561 now available that, during increased muscle activity, the reduction in inhibition is selective and  
562 specific to the agonist muscle. This supports the findings of Mason et al. (2017a) whereby  
563 ipsilateral changes in inhibition were confined to the agonist muscle following cross-education.

564 To date, there has only been one cross-education study that has examined LICI (Manca  
565 et al. 2016a). Participants trained the first dorsal interosseous (FDI) muscle via a maximal  
566 pinch-force task (five sets of ten repetitions) three days a week for four-weeks. Following  
567 training, there were no changes in LICI, but the corticospinal silent period was not measured.  
568 Based upon the current systematic evidence available, in order to increase our understanding  
569 of the corticospinal responses to cross-education, there is a need to design cross-education  
570 studies that use techniques to probe both the excitatory and inhibitory cortico-cortical  
571 connections following both acute and chronic interventions. These will provide important  
572 information about the mechanisms associated with cross-education.

### 573 *Interhemispheric inhibition and cross-education*

574 TMS can be used to assess the mediating inhibitory pathways between cerebral  
575 hemispheres via IHI. IHI is a neurological mechanism whereby one hemisphere inhibits the  
576 opposite hemisphere and its presence is due to excitatory pathways via the corpus callosum  
577 which synapse onto local inhibitory circuits within the target M1 (Perez and Cohen 2009).  
578 Eight-weeks of maximal isometric training of the right FDI reduced IHI from the trained to the  
579 untrained M1 by 31% and, importantly, this increase was associated with the magnitude of  
580 cross-education (Hortobágyi et al. 2011). This finding supports the evidence from the  
581 examination of IHI following strong unilateral contractions and acute motor-skill training  
582 (Hortobágyi et al. 2003; Perez et al. 2007c). However, Manca et al. (2016a) recently reported  
583 that four weeks of cross-education had no effect on IHI. Currently, it is inconclusive whether



584 reductions in IHI mediate cross-education, but the physiological role of IHI seems to be an  
585 important modulator for cross-education. For example, one hypothesis suggests that reduced  
586 IHI from the trained to the untrained M1 would support the theory of cross-activation from the  
587 active to the non-active M1 (Lee et al. 2010), a mechanism consistently reported during  
588 maximal contraction of one limb (Hortobágyi et al. 2003) and implicated in cross-education  
589 (Frazer et al. 2017; Hendy and Kidgell 2014; Hendy et al. 2015; Mason et al. 2017a; Ruddy et  
590 al. 2017).

591           Collectively, the use of TMS to examine the ipsilateral corticospinal responses to cross-  
592 education has begun to provide some putative neural mechanisms that mediate a change in  
593 strength of an untrained limb. However, there is a need to establish whether there is a direct  
594 relationship between the changes in ipsilateral corticospinal responses and the magnitude of  
595 cross-education. Thus, at present, it remains tentative whether the changes in ipsilateral TMS  
596 responses actually underpin the observed changes in strength of the untrained limb.  
597 Furthermore, because of the limitations associated with TMS and the anatomy of the  
598 corticospinal tract, changes in the excitability of the spinal cord and the ability to activate the  
599 motoneurone pool (i.e., voluntary activation) may also add further insights into the ipsilateral  
600 corticospinal responses associated with cross-education.

601

## 602 **Potential spinal mechanisms and cross-education**

603           There is evidence to suggest that adaptations in spinal circuitry occur following strength  
604 training (Duclay et al. 2008); however, current methodology is unable to determine specific  
605 spinal pathways that may be involved in the cross-education of strength (Dragert et al. 2011;  
606 Fimland et al. 2009; Lagerquist et al. 2006). Despite this, the Hoffman reflex (H-reflex), an  
607 electrically evoked reflex used to quantify the efficacy of the 1a afferent motoneuronal synapse

608 (Palmeri et al. 2004), has been measured in only three cross-education studies (Dragert et al.  
609 2011; Fimland et al. 2009; Lagerquist et al. 2006). All three studies showed no change in H-  
610 reflex amplitude following cross-education. Thus, these findings do not enable any definitive  
611 conclusions to be drawn as to whether the intrinsic circuitry of the spinal cord contributes to  
612 the cross-education of strength.

613

#### 614 **Twitch force studies and cross-education**

615 The interpolated twitch technique has been used extensively to measure voluntary  
616 activation as a reflection of “neural drive” (Merton 1954). In addition to measuring sEMG  
617 changes with unilateral and contralateral musculature following training, twitch interpolation  
618 (or interpolated twitch technique) is a single-pulse protocol that allows investigations to  
619 address the question of training protocols increasing central nervous system excitability. In  
620 particular, twitch interpolation allows for the investigation of whether the motoneurone pool  
621 has been excited sufficiently by volition to evoke all the force the relevant muscle can produce  
622 (Herbert and Gandevia 1999; Gandevia, 2001; Todd et al. 2016). The amplitude of the  
623 interpolated twitch declines with increasing contraction intensity (voluntary activation)  
624 allowing for the quantification of the level of excitation of motoneurons, or “neural drive”  
625 (Herbert and Gandevia 1999).

626 Historically, understanding the neural mechanisms contributing to strength changes  
627 following strength training has been conducted in the primary agonist muscle (see review by  
628 Shield and Shi 2004). However, electrical twitch interpolation has also been used to assess  
629 neural adaptation in contralateral neural pathways following unilateral strength training (cross-  
630 education; see Table 3). For example, Shima et al. (2002) showed that, in healthy untrained  
631 males (n=9), voluntary activation increased in both trained and contralateral untrained leg

632 (plantar flexor muscles) following a six-week training period of progressive strength training  
633 of calf raises and foot-presses. Moreover, following a six-week period of detraining, the authors  
634 found that voluntary activation did not significantly change (trained:  $0.3 \pm 2.6\%$ ; contralateral:  
635  $-0.7 \pm 1.7\%$ ), suggesting that cross education of muscular strength might be explained by  
636 central neural mechanisms during training and, at least in part, during the period of detraining  
637 (Shima et al. 2002).

638 More recently, twitch interpolation has been used to assess neural adaptations with  
639 strength training in older populations (Tøien et al. 2017). Whilst it is known that age can  
640 attenuate efferent neural drive, even in those with a long history of strength training experience,  
641 these authors investigated whether the deterioration of neural drive impedes contralateral  
642 neural drive with increasing age (Molenaar et al. 2013). They used an older population of males  
643 ( $n = 23$ ; mean age  $73 \pm 4$  years) who undertook a three-week strength training program (nine  
644 sessions; three sessions per week) of dynamic plantar flexion involving both concentric and  
645 eccentric contractions (90% of one-repetition maximum [1RM]). Voluntary activation,  
646 measured in the contralateral soleus muscle, increased by a mean of  $5.0 \pm 5.5\%$ . Tøien et al.  
647 (2017) suggested that older individuals exhibit cross-limb neural adaptations, providing a  
648 potential clinical value in unilateral high-intensity strength-training that is not limited by age.

649 Whilst the majority of studies using interpolated twitch technique are undertaken  
650 electrically, magnetic stimulation may also be used (Lampropoulou et al. 2012). Since 2000,  
651 there has been increased interest in using peripheral magnetic stimulation as an alternative to  
652 electrical stimulation in assessing voluntary activation (Goodall et al. 2014) in upper-limb  
653 (Harris et al. 2000; Lampropoulou et al. 2012) and lower-limb musculature (Goodall et al. 2009;  
654 Hamnegård et al. 2004; Kremenic et al. 2004; Vivodtzev et al. 2005). Comparisons between  
655 electrical and magnetic peripheral twitch interpolation during maximal voluntary contractions  
656 show similarities in the onset latencies and supramaximal twitch response in hand muscles

657 (Harris et al. 2000; Olney et al. 1990) and also in biceps brachii (Lampropoulou et al. 2012).  
658 However, peripheral twitch interpolation is limited because the exact level (or site) of  
659 adaptation within the central nervous system cannot be distinguished as the change may occur  
660 at any point, or combination of points, proximal to the position of stimulation (Goodall et al.  
661 2014). Further, it has been argued that other limitations of peripheral stimulation, including the  
662 strength of the stimulus, can pose problems in terms of the distribution of the magnetic field,  
663 particularly if it is too high (supramaximal stimulus) and the spread of the magnetic field can  
664 conduct to tissues other than the target peripheral nerve (Hamnegård et al. 2004; Matsumoto et  
665 al. 2010; Millet et al. 2011). Conversely, the stimulus might not be of sufficient intensity if the  
666 coil position is not correctly orientated (Lampropoulou et al. 2012) to maximally stimulate all  
667 motor units, a desired outcome that might also be limited by subcutaneous adipose tissue (Lin  
668 et al. 2008; Tomazin et al. 2010, 2011). As a result, peripheral magnetic stimulation does not  
669 have extensive recognition either as a ‘gold standard’ technique or as a practical alternative to  
670 electrical twitch interpolation (Lampropoulou et al. 2012).

671 Magnetic stimulation has also been shown to elicit a twitch response when stimulation is  
672 applied over the M1. There are many studies that utilise TMS to quantify adaptations of the  
673 corticospinal pathway following short-term strength-training, not only in the trained (Kidgell  
674 and Pearce 2010; Kidgell et al. 2010; Leung et al. 2017; Mason et al. 2017b; Weier et al. 2012)  
675 but also in the untrained contralateral arm (Coombs et al. 2016; Kidgell et al. 2011, 2015) and  
676 leg (Goodwill and Kidgell 2012; Goodwill et al. 2012; Latella et al. 2012). However, these  
677 studies generally used sub-maximal contractions to measure MEPs and corticospinal silent  
678 period as determinants of neural adaptations in the contralateral untrained limb. While maximal  
679 voluntary activation of human elbow-flexors can be assessed with TMS ( $VA_{TMS}$ ) (Todd et al.  
680 2004), few studies have employed the technique of  $VA_{TMS}$  to assess the neural adaptations to  
681 cross-education (Lee et al. 2009b). This is surprising because an advantage of  $VA_{TMS}$  is that it

682 allows the assessment of supraspinal contributions for the volitional drive to the muscle during  
683 a maximal contraction (Lee et al. 2008). However, the technique itself is technically difficult  
684 and has its own limitations. For example, it is imperative that the TMS stimulus produces a  
685 maximal response in the target muscle (Carroll et al. 2008). In addition, changes in  $VA_{TMS}$  are  
686 likely to be more specific to the testing condition (e.g., isometric), thus training interventions  
687 that do not match the conditions of testing prove problematic when interpreting the data.

688 Despite the theoretical contribution of  $VA_{TMS}$ , there is a paucity of research using this  
689 technique, particularly for contralateral neural adaptations following cross-education strength  
690 training. To date, only one study has utilized TMS twitch interpolation to assess neural  
691 adaptations in the contralateral arm (Lee et al. 2009b). Following four weeks of unilateral wrist  
692 extension strength training, a significant increase in contralateral voluntary activation in the  
693 untrained wrist was observed ( $2.9 \pm 3.5\%$ ). These authors concluded that unilateral maximal  
694 strength training improved motor output from the M1 to the homologous untrained muscles.  
695 Given the potential of using  $VA_{TMS}$  to assess the ability of the M1 to drive the motoneurone  
696 pool, future studies should consider incorporating this technique.

697

### 698 **Interventions to enhance the cross-education effect**

699 Recently, there have been some innovative techniques used to enhance the cross-  
700 education effect. There is now some preliminary evidence to show that the cross-education of  
701 strength may be enhanced by mirror feedback. This intervention activates the mirror neuron  
702 system (MNS) which is known to have projections to motor regions (Zult et al. 2014). In  
703 addition, there are emerging studies that have used tDCS, a simple and cost effective technique  
704 whereby electrodes are placed over the M1 of a target muscle and low levels of electricity are  
705 passed through to the underlying cortical neurones (Frazer et al. 2017). Both acute and chronic

706 studies now show that the cross-education of strength is enhanced when tDCS is applied to the  
707 ipsilateral M1 before or during the training intervention (Frazer et al. 2017; Hendy and Kidgell  
708 2014; Hendy et al. 2015). In a similar manner, applying electrical stimulation over the training  
709 muscles (Hortobágyi et al. 1999) and whole-body vibration training (WBV) have also been  
710 used to enhance the cross-education effect (Goodwill and Kidgell 2012; Lapole et al. 2013).

### 711 ***Mirror neurones and mirror box training to augment cross-education***

712 The aforementioned work reporting cross-education of strength is compelling. When  
713 coupled with evidence showing that this phenomenon can attenuate strength loss and reduce  
714 the magnitude of atrophy during short-term immobilisation in healthy individuals with  
715 (Magnus et al. 2013) and without (Farthing et al. 2009, 2011; Pearce et al. 2012) a fracture,  
716 this opens up exciting possibilities for cross-education as a therapeutic intervention in clinical  
717 populations with unilateral orthopaedic and neurological dysfunction. These preliminary data  
718 are promising, but many clinical populations have unilateral dysfunction for periods of time  
719 more extended than those studied in the literature. Consequently, cross-education might not be  
720 as efficacious in some scenarios. Given the potential clinical importance of cross-education, it  
721 would be of interest to explore methods that have the potential to further augment the  
722 magnitude of the cross-education of muscle strength. Because sensory feedback during motor  
723 practice can increase motor output, one possibility is to activate neurones involved in the  
724 transfer that might also be activated by other means, thereby resulting in a synergistic effect on  
725 motor output and, hence, increase the transfer of strength (Howatson et al. 2013).

726 Previous research (Carson and Ruddy 2012; Farthing et al. 2007, 2011; Hortobágyi et  
727 al. 2011) has shown that, following strength training and the subsequent cross-education, there  
728 is overlap in the activation of brain areas that contain mirror neurones. The MNS is a network  
729 of neurones that are active during perceptual and actual execution of motor activities (Iacoboni  
730 1999, 2005; Rizzolatti et al. 1996). In a recent hypothesis (Howatson et al. 2013) and systematic

731 review (Zult et al. 2014), the possibility of activating the MNS concurrently with performing a  
732 cross-education strength task was proposed to increase the magnitude of cross-education.

733         The MNS is distributed across numerous areas of the cerebral cortex and provides a  
734 neuroanatomical basis for ‘action observation’ whereby observation and/or imitation of an act  
735 can develop motor learning and skill acquisition (Rizzolatti et al. 1999; Sakadjian et al. 2014).  
736 In brief, it is thought that the MNS is activated when performing a similar task that has been  
737 observed. Specifically, the MNS is activated during the observation of a self-performed act,  
738 observing a third person, imitation of an observed task, perceptual input and the performance  
739 of the practised movement (di Pellegrino et al. 1992; Heyes 2010; Ray and Heyes 2011). These  
740 activities are very common in the arts and athletic performance where extensive observed  
741 practice is used to master skills that stimulate areas common to motor cortical areas and the  
742 MNS which are detailed elsewhere (Howatson et al. 2013; Zult et al. 2014). Previous  
743 experience of the motor activity seems important to modulate and engage the MNS (Beudel et  
744 al. 2011); naïve participants, when compared to skilled dancers and musicians, show greater  
745 MNS activation when observing dancers and musicians, respectively (Heyes 2010). Therefore,  
746 practice of a task will likely engage these neural networks and improve motor performance  
747 (Howatson et al. 2013; Zult et al. 2014).

748         Conceptually, the observation of a relatively simple, self-performed, unilateral motor-  
749 task (like resistance exercise) might enhance the cross-education effect by viewing the  
750 performed task in a mirror. In this concept, a reflected image (with the use of a mirror) is  
751 superimposed over the non-exercising limb to provide the illusion that the non-active limb is  
752 moving. The reality is that the participant is actually viewing a reflection of the exercising limb  
753 and, hence, receives the visual sensation of the non-active limb actually moving (Nojima et al.  
754 2012; Small et al. 2012). Previous work using mirror training showed increased ipsilateral brain  
755 activity (Garry et al. 2005; Matthys et al. 2009), skill acquisition of the non-practised hand in

756 healthy participants (Hamzei et al. 2012; Lappchen et al. 2012; Nojima et al. 2012), reduced  
757 phantom-limb pain (Ramachandran and Rogers-Ramachandran 1996), and enhanced stroke  
758 recovery (Sutbeyaz et al. 2007; Yavuzer et al. 2008). The brain structures thought to be  
759 implicated in cross-education have neuroanatomical commonality with those of the MNS. This  
760 makes the expectation tenable that observing the moving limb in a mirror could increase the  
761 brain activity controlling the resting limb and, thereby, increase the magnitude of cross-  
762 education (Howatson et al. 2013; Zult et al. 2014). Until recently, this idea had not been  
763 explored experimentally.

764 In two subsequent studies arising from the aforementioned concept, we explored the  
765 cortical excitability and intra and interhemispheric connectivity: 1) when observing forceful  
766 contractions in a mirror; and 2) to assess the magnitude of cross-education when resistance  
767 training was performed using a mirror. The first of these studies (Zult et al. 2015) was cross-  
768 sectional in nature to examine the cortical networks hypothesised to share commonality  
769 between the MNS and networks thought to be involved in cross-education. In this work, 27  
770 right-handed male volunteers had corticospinal and motor-cortical responses to TMS recorded  
771 in the left flexor carpi radialis (FCR). This was done with and without viewing a mirror, at rest  
772 and during a forceful shortening contraction of the right-wrist flexors. Corticospinal  
773 excitability in the resting FCR increased during the contraction (similar to that observed  
774 previously) but was not different between mirror and no-mirror conditions. However, SICI was  
775 significantly lower (~9% release of SICI) illustrating that GABA-ergic inhibitory networks  
776 were implicated in the cross-education phenomenon (Goodwill et al. 2012; Perez and Cohen  
777 2008). This first step in support of the hypothesis (Howatson et al. 2013) provided evidence  
778 that neural networks implicated in cross-education can also be modulated by viewing a  
779 reflection of the exercising limb superimposed on the resting limb. In a follow-up training study  
780 that further tested this idea, Zult and colleagues (2016) took 24 right-handed volunteers to



781 undertake either mirror training or no-mirror training. Specifically, all participants completed  
782 15 resistance-training bouts (six sets of eight repetitions isokinetic, concentric actions [20°/s]  
783 at 80% MVC) of the right-wrist flexors over a three-week period. Critically, the training  
784 resulted in improved performance in both groups, but the mirror group had a 13% greater  
785 increase ( $P = 0.03$ ) than the no-mirror group in strength of the untrained limb. These strength  
786 improvements in the untrained limb were accompanied with a mean reduction in the  
787 contralateral silent period of 30 ms, which was thought to be indicative of greater inhibition of  
788 GABA<sub>B</sub>-mediated networks. In addition, there were reductions in interhemispheric inhibition,  
789 a GABA-ergic network between cortical hemispheres which is also implicated in the MNS  
790 from a neuroanatomical perspective (Zult et al. 2014).

791         Although the potential for using a mirror to augment the cross-education effect is just  
792 emerging, it provides a potentially exciting field of research. Volunteers in these studies (Zult  
793 et al. 2015, 2016) verbally reported sensations of the left, non-active limb moving when  
794 observing strong monotonic contractions of the right limb in a mirror that were superimposed  
795 on the non-active limb. So, conceptually, there could be a placebo effect that has limited the  
796 neurophysiological basis (at least in the measure collected). Notwithstanding, these data are  
797 particularly important because of the implications for clinical populations, whereby an increase  
798 in the cross-education phenomenon is amplified. This effect should be investigated further to  
799 explore its application to unilateral orthopaedic or neurological impairment. Importantly, the  
800 use of neuroimaging techniques to establish the role of the MNS and other regions of the  
801 cerebral cortex seems to be an important progression in understanding the mediating  
802 mechanisms of cross-education (Rizzolatti and Craighero 2004).

803 ***Transcranial direct current stimulation and cross-education***

804 tDCS has emerged as a promising, non-invasive technique to improve motor  
805 performance in both young and older adults (Goodwill et al. 2015; Kidgell et al. 2013). The  
806 application of tDCS over the M1 induces transient, polarity-specific changes in the neuronal  
807 resting membrane potential (Nitsche et al. 2008), with increases in excitability and performance  
808 improvements lasting up to 90 min following the cessation of stimulation (Lang et al. 2005).  
809 However, similar to the TMS strength-training studies (Kidgell et al. 2017), the reproducibility  
810 of neuroplasticity inducing protocols, like tDCS, remains a challenge (Heroux et al., 2015;  
811 Heroux et al., 2017). However, recently, tDCS has been used experimentally to enhance the  
812 cross-education of muscle strength. For example, Hendy and Kidgell (2014) reported an  
813 increase in maximal strength and cross-activation of the contralateral untrained limb (left hand)  
814 following a single session of anodal tDCS applied to the ipsilateral right M1 during strength  
815 training of the right hand (Hendy and Kidgell 2014). In a follow-up study, Hendy et al. (2015)  
816 applied anodal tDCS to the ipsilateral right M1 during a two-week strength-training  
817 intervention and showed that the effects of cross-education were prolonged, and that tDCS  
818 retained strength of the untrained limb compared to sham tDCS and strength-training (Hendy  
819 et al. 2015).

820 Although this data is interesting and has potential applications in the clinical  
821 environment, there is a greater need to identify the optimal timing of tDCS to the ipsilateral  
822 M1 (i.e., before, during or after training). In an attempt to address this, we recently  
823 demonstrated a substantial increase in maximum strength of the untrained left biceps brachii  
824 when anodal tDCS was applied to the ipsilateral M1 (right hemisphere), prior to a single bout  
825 of strength training of the right arm only, exploiting the principles of homeostatic meta-  
826 plasticity (Frazer et al. 2017). Although preliminary evidence indicates that tDCS is a  
827 promising tool, the timing of application needs to be rigorously investigated following both  
828 single-session and longer-term training periods (>2 weeks). Undoubtedly, combining robust

829 investigation techniques, such as TMS and fMRI, would aid in quantifying the potential  
830 opportunity to augment the cross-education of muscle strength.

### 831 *Electromyostimulation during cross-education*

832         Similar to voluntary contractions evoked during unilateral strength training, there is  
833 good evidence to show that the application of electrostimulation during strength training  
834 increases MVC force production of an untrained homologous muscle following unilateral  
835 strength training (Bezerra et al. 2009; Hortobágyi et al. 1999). There are now several studies  
836 that have revealed electrical stimulation of a muscle, compared with voluntary contraction,  
837 evokes specific effects at the level of the cerebral cortex and increases force in an untrained  
838 limb (Bezerra et al. 2009; Hortobágyi et al. 1999). Hortobágyi et al. (1999) reported that  
839 electrical muscle stimulation induced a contralateral increase in strength of 21% following  
840 four-weeks of isometric strength training, which was comparable to that induced by voluntary  
841 isometric strength training alone. In addition, six weeks of eccentric strength training with  
842 electrical muscle stimulation induced an increase in strength of 104% compared to 23% for  
843 voluntary eccentric training alone (Hortobágyi et al. 1999; Oakman et al. 1999). Interestingly,  
844 electrical stimulation training is also more effective than voluntary strength training when  
845 imparting a cross-education effect (Bezerra et al. 2009). Because the cross-education effect  
846 following electrical stimulation training is not associated with any changes in the cross-  
847 sectional area of the contralateral untrained muscle (Bezerra et al. 2009), the physiological  
848 mechanisms underpinning the changes in strength seem to reside within the cerebral cortex.  
849 For example, when electrical muscle stimulation is used to induce left-wrist flexion, both TMS  
850 induced MEPs and the H-reflex increase in the right resting-wrist flexors (Hortobágyi et al.  
851 2003). In a similar manner, when electrical muscle stimulation is applied during voluntary  
852 contraction of the left-wrist flexors, TMS-induced MEPs are increased, but the H-reflex in the  
853 right resting-wrist flexors is reduced (Hortobágyi et al. 2003). These observations suggest that

854 electrical muscle stimulation and voluntary contractions are affected differently at a supraspinal  
855 level in contralateral homologous muscles. This difference is likely the result of increased  
856 sensory and nociceptive inputs that act at a cortical level following electrical stimulation.  
857 Perhaps such inputs modify motor output and interhemispheric paths, which lead to an increase  
858 in strength of the trained and untrained limb. Certainly, this hypothesis is supported by changes  
859 in IHI following unilateral training (Hortobágyi et al. 2011; Howatson et al. 2011; Lee et al.  
860 2010).

### 861 *Whole-body vibration training and cross-education*

862 The recent emergence of WBV as a training technique has been of interest to  
863 researchers due to its potential to improve neuromuscular function. Many studies have reported  
864 increases in strength following an acute bout of WBV. Similarly, increases in strength have  
865 also been demonstrated following a period of strength training with the addition of WBV  
866 (Issurin 2005; Nordlund and Thorstensson 2007; Rittweger 2010), suggesting that WBV  
867 training may be an effective and alternative training technique for strength development  
868 (Rittweger et al. 2003) and for enhancing cross-education (Goodwill and Kidgell 2012). Given  
869 that the magnitude of strength gain in the trained limb is an important proxy for strength transfer  
870 to the untrained limb, we recently examined the effect of unilateral strength training with  
871 superimposed WBV on the magnitude of cross-education (Goodwill and Kidgell 2012).  
872 Healthy participants completed unilateral strength training with or without the application of  
873 WBV (35 Hz; 2.5 mm amplitude), three times per week for three weeks. Strength increased by  
874 41% in the trained limb following strength training without WBV and by 55% with WBV.  
875 Interestingly, the cross-transfer of strength was greater for the untrained limb (52%) following  
876 WBV, with only a 35% transfer following training without WBV. Further, after WBV training,  
877 there was an increase in corticospinal excitability and a reduction in SICI of the ipsilateral M1  
878 suggesting that WBV training had a cortical effect (Goodwill and Kidgell 2012). In a similar

879 manner, 14 days of Achilles-tendon vibration also increased the strength of a vibrated  
880 gastrocnemius and the non-vibrated gastrocnemius muscle. The increase in strength of the non-  
881 vibrated gastrocnemius was associated with a 41% increase in the volitional wave (a measure  
882 of neural drive), but the H-reflex remained unchanged (Lapole et al. 2013). These observations  
883 suggest that there could be additional cross-education benefits following the application of  
884 vibration to the training limb.

885

### 886 **Clinical application of cross-education**

887 In clinical practice, unilateral injuries, such as knee osteoarthritis, tendinopathy,  
888 fracture, stroke, and cerebral palsy are extremely common. In the Western world, 6% of women  
889 will have sustained a distal radius fracture by the age of 80, and 9% by the age of 90. Regardless  
890 of whether these fractures are treated surgically or by casting, patients are immobilised for two  
891 to six weeks (or more). Physical and occupational therapy, as a key element in rehabilitation,  
892 typically only starts following the period of immobilisation. During the period of  
893 immobilisation, patients often keep their injured limb in rigid postures, and the involved  
894 ligaments of the joints become shortened (Freeland and Lubert 2005). Different methods of  
895 treatment, but especially the long immobilisation periods, lead to a high incidence of  
896 complications which are typically associated with poor functional outcomes (McKay et al.  
897 2001). These complications include complex and regional pain syndrome, stiffness, nerve  
898 injury, tendon and ligament injuries, and a large reduction in range of motion and muscle  
899 strength (Diaz-Garcia et al. 2011). In addition, recovery of the strength loss and muscle atrophy  
900 experienced following a unilateral injury and period of immobilisation is often hampered by  
901 patients' and therapists' inability to effectively exercise the involved body part. As a result,  
902 final function of the injured limb is often suboptimal, highlighting the critical need to

903 implement strategies such as cross-education to attenuate the loss of function that occurs with  
904 immobilisation.

905         Although there is a strong consensus that unilateral motor practice is a viable candidate  
906 to reduce unilateral loss of muscle strength and motor function during a period of  
907 immobilisation, there is limited evidence to support this notion. To date, just five studies have  
908 investigated the effects of cross-education in healthy participants undergoing a period of  
909 immobilisation (Andrushko et al. 2017; Farthing et al. 2009, 2011; Papandreou et al. 2013;  
910 Pearce et al. 2012). All five investigations found that a cross-education intervention attenuated  
911 the strength loss in the immobilised limb, with four of the investigations also displaying a  
912 sparing effect for muscle size (Andrushko et al. 2017; Farthing 2009; Papandreou et al. 2013;  
913 Pearce et al. 2012). Of particular interest, this cross-education model was successfully  
914 translated into a clinical population of women older than 50 years who suffered a unilateral  
915 distal radius fracture (Magnus et al. 2013). Magnus et al. (2013) demonstrated an increase in  
916 strength and range of motion of injured wrists 12-weeks post-fracture, providing preliminary  
917 evidence of the clinical efficacy of cross-education for immobilised patients. Nevertheless,  
918 there is still insufficient empirical evidence demonstrating that unilateral training of the non-  
919 injured limb during the early rehabilitation period can attenuate atrophy and strength loss  
920 associated with immobilisation. The successful implementation of such an intervention, and  
921 subsequent exploitation of the cross-education effect, could accelerate recovery by enabling  
922 patients to maintain a higher level of function in the injured limb prior to remobilisation. This  
923 would have the dual benefit of improving functional outcomes in the immediate period post-  
924 injury and facilitating the execution of rehabilitation exercises designed to mobilise, reduce  
925 atrophy and strengthen the injured limb.

926         Another highly-plausible application of cross-education is the restoration of bilateral  
927 limb symmetry following stroke (Dragert and Zehr 2013). A recent meta-analysis has shown

928 the positive effect of cross-education on muscle strength in patients who have suffered a stroke  
929 (Ehrensberger et al. 2016). Although only two studies were analysed, post-stroke hemiplegic  
930 patients demonstrated a 31.4% and 45.5% strength increase in the untrained, more-affected  
931 dorsiflexor muscle following unilateral training (Dragert and Zehr 2013; Kim et al. 2015).  
932 Indeed, these results are promising; however, attention needs to shift beyond the focus of  
933 demonstrating a transfer in strength to gains in functional tasks and recovery of motor function  
934 (Ehrensberger et al. 2016). Furthermore, there has been recent preliminary evidence suggesting  
935 that cross-education might aid in the management of limbs severely weakened because of  
936 multiple sclerosis (Dragert and Zehr 2013; Manca et al. 2016b, 2017b). Of note, none of the  
937 trials investigating the efficacy of cross-education in neurological patients employed a training  
938 design using eccentric or dynamic contraction modes. Given the recent finding that eccentric  
939 and dynamic contractions induce significantly greater contralateral gains in strength in healthy  
940 subjects (Manca et al. 2017a), it would be interesting to examine whether the transfer of  
941 strength in neurological subjects may be further enhanced by changing the type of training  
942 contraction employed. This highlights the urgency to not only investigate the role of cross-  
943 education in the rehabilitation and management of neurological patients, but also to further  
944 enhance our understanding of best prescription variables for this population. Overall, there is a  
945 great need to examine the efficacy of cross-education in clinical populations with an emphasis  
946 on using interventions which are known to maximise the cross-education effect.

947

## 948 **General summary and conclusions**

949 Cross-education is a phenomenon that has been shown to occur following different  
950 unilateral strength-training interventions. Although some variability exists regarding the  
951 magnitude of the cross-education effect between the upper and lower limbs, critically, there is

952 a lack of correlation between the reported cross-education effect and the changes in the nervous  
953 system. Overall, it seems that the neural adaptations to cross-education of muscular strength  
954 most likely represent a continuum of change within the central nervous system that involves  
955 both structural and functional changes within cortical motor and non-motor regions. Such  
956 changes are likely to be the result of more subtle changes along the entire neuroaxis which  
957 include increased corticospinal excitability, reduced cortical inhibition, reduced IHI, changes  
958 in V<sub>A</sub>TMS and new regions of cortical activation (see Fig. 1).

959 *Insert Figure 1.*

960 Notwithstanding, there is a need to widen the breadth of research that collectively  
961 employs several neurophysiological techniques to better understand the potential mechanisms  
962 mediating cross-education. This fundamental step is required in order to better prescribe  
963 targeted and effective guidelines for the clinical practice of cross-education. There is a need to  
964 determine whether similar cortical responses also occur in clinical populations where, perhaps,  
965 the benefits of cross-education could be of most benefit.

966

967



968 **References:**

- 969 Abazović E, Kovačević E, Kovač S, Bradić J (2015) The effect of training of the non-dominant  
970 knee muscles on ipsi- and contralateral strength gains. *Isokinet Exerc Sci* 23:177-182.
- 971 Alawieh A, Tomlinson S, Adkins D, Kautz S, Feng W (2017) Preclinical and clinical evidence  
972 on ipsilateral corticospinal projections: Implication for motor recovery. *Trans Stroke*  
973 *Res* 8:529-540.
- 974 Allen GM, McKenzie DK, Gandevia SC (1998) Twitch interpolation of the elbow flexor  
975 muscles at high forces. *Muscle & Nerve* 21:318-328.
- 976 Andrushko JW, Lanovaz JL, Björkman KM, Kontulainen SA, Farthing JP (2017) Unilateral  
977 strength training leads to muscle-specific sparing effects during opposite homologous  
978 limb immobilization. *J Appl Physiol* doi:10.1152/jappphysiol.00971.2017.
- 979 Beudel M, Zijlstra S, Mulder T, Zijdewind I, de Jong BM (2011) Secondary sensory area SII  
980 is crucially involved in the preparation of familiar movements compared to movements  
981 never made before. *Hum Brain Mapp* 32:564-579.
- 982 Bezerra P, Zhou S, Crowley Z, Brooks L, Hooper A (2009) Effects of unilateral  
983 electromyostimulation superimposed on voluntary training on strength and cross-  
984 sectional area. *Muscle Nerve* 40:430-437.
- 985 Brinkman J, Kuypers HG (1973) Cerebral control of contralateral and ipsilateral arm, hand and  
986 finger movements in the split-brain rhesus monkey. *Brain* 96:653-674.
- 987 Bunday Karen L, Perez Monica A (2012) Motor recovery after spinal cord injury enhanced by  
988 strengthening corticospinal synaptic transmission. *Curr Biol* 22:2355-2361.
- 989 Cannon RJ, Cafarelli E (1987) Neuromuscular adaptations to training. *J Appl Physiol* 63:2396-  
990 2402.
- 991 Carolan B, Cafarelli E (1992) Adaptations in coactivation after isometric resistance training. *J*  
992 *Appl Physiol* 73:911-917.

993 Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC (2006) Contralateral effects of unilateral  
994 strength training: evidence and possible mechanisms. *J Appl Physiol* 101:1514-1522.

995 Carson RG (2005) Neural pathways mediating bilateral interactions between the upper limbs.  
996 *Brain Res Brain Res Rev* 49:641-662.

997 Carson RG, Ruddy KL (2012) Vision Modulates Corticospinal Suppression in a Functionally  
998 Specific Manner during Movement of the Opposite Limb. *J Neurosci* 32:646-652.

999 Christie A, Kamen G (2013) Cortical inhibition is reduced following short-term training in  
1000 young and older adults. *AGE* 1-10.

1001 Clark BC, Issac LC, Lane JL, Damron LA, Hoffman RL (2008) Neuromuscular plasticity  
1002 during and following 3 wk of human forearm cast immobilization. *J Appl Physiol*  
1003 105:868-878.

1004 Clark BC, Mahato NK, Nakazawa M, Law TD, Thomas JS (2014) The power of the mind: the  
1005 cortex as a critical determinant of muscle strength/weakness. *J Neurophysiol* 112:3219-  
1006 3226.

1007 Coombs TA, Frazer AK, Horvath DM, Pearce AJ, Howatson G, Kidgell DJ (2016) Cross-  
1008 education of wrist extensor strength is not influenced by non-dominant training in right-  
1009 handers. *Eur J Appl Physiol* 116:1757-1769.

1010 Coratella G, Milanese C, Schena F (2015) Cross-education effect after unilateral eccentric-only  
1011 isokinetic vs dynamic constant external resistance training. *Sport Sci Health* 11:329-  
1012 335.

1013 Cordes D et al. (2001) Frequencies Contributing to Functional Connectivity in the Cerebral  
1014 Cortex in “Resting-state” Data. *Am J Neuroradiol* 22:1326-1333.

1015 Dettmers C et al. (1995) Relation between cerebral activity and force in the motor areas of the  
1016 human brain. *J Neurophysiol* 74:802-815.

1017 Di Lazzaro V et al. (1998) Effects of voluntary contraction on descending volleys evoked by  
1018 transcranial stimulation in conscious humans. *J Physiol* 508 ( Pt 2):625-633.

1019 Di Lazzaro V, Oliviero A, Profice P, Ferrara L, Saturno E, Pilato F, Tonali P (1999) The  
1020 diagnostic value of motor evoked potentials. *Clin Neurophysiol* 110:1297-1307.

1021 di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G (1992) Understanding motor  
1022 events: a neurophysiological study. *Exp Brain Res* 91:176-180.

1023 Diaz-Garcia R, Oda T, Shauver M, Chung K (2011) A systematic review of outcomes and  
1024 complications of treating unstable distal radius fractures in the elderly. *J Hand Surg*  
1025 36:824-835.

1026 Dragert K, Zehr E (2011) Bilateral neuromuscular plasticity from unilateral training of the  
1027 ankle dorsiflexors. *Exp Brain Res* 208:217-227.

1028 Dragert K, Zehr EP (2013) High-intensity unilateral dorsiflexor resistance training results in  
1029 bilateral neuromuscular plasticity after stroke. *Exp Brain Res* 225:93-104.

1030 Duchateau J, Semmler JG, Enoka RM (2006) Training adaptations in the behavior of human  
1031 motor units. *J Appl Physiol* 101:1766-1775.

1032 Duclay J, Martin A, Robbe A, Pousson M (2008) Spinal reflex plasticity during maximal  
1033 dynamic contractions after eccentric training. *Med Sci Sports Exerc* 40:722-734.

1034 Dum RP, Strick PL (2005) Frontal Lobe Inputs to the Digit Representations of the Motor Areas  
1035 on the Lateral Surface of the Hemisphere. *J Neurosci* 25:1375-1386.

1036 Ehrensberger M, Simpson D, Broderick P, Monaghan K (2016) Cross-education of strength  
1037 has a positive impact on post-stroke rehabilitation: a systematic literature review. *Top*  
1038 *Stroke Rehabil* 23:126-135.

1039 Farthing JP (2009) Cross-Education of Strength Depends on Limb Dominance: Implications  
1040 for Theory and Application. *Exerc Sport Sci Rev* 37:179-187.

1041 Farthing JP, Borowsky R, Chilibeck PD, Binsted G, Sarty GE (2007) Neuro-Physiological  
1042 Adaptations Associated with Cross-Education of Strength. *Brain Topogr* 20:77-88.

1043 Farthing JP, Chilibeck PD (2003) The effect of eccentric training at different velocities on  
1044 cross-education. *Eur J Appl Physiol* 89:570-577.

1045 Farthing J, Chilibeck PD (2005) Cross-education of arm muscular strength is unidirectional in  
1046 right-handed individuals. *Med Sci Sports Exerc* 37:1594-1600.

1047 Farthing JP, Krentz JR, Magnus CRA (2009) Strength training the free limb attenuates strength  
1048 loss during unilateral immobilization. *J Appl Physiol* 106:830-836.

1049 Farthing JP et al. (2011) Changes in Functional Magnetic Resonance Imaging Cortical  
1050 Activation with Cross Education to an Immobilized Limb. *Med Sci Sports Exerc*  
1051 43:1394-1405.

1052 Fimland M, Helgerud J, Solstad G, Iversen V, Leivseth G, Hoff J (2009) Neural adaptations  
1053 underlying cross-education after unilateral strength training. *Eur J Appl Physiol*  
1054 107:723-730.

1055 Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD (2011)  
1056 Differential Callosal Contributions to Bimanual Control in Young and Older Adults. *J*  
1057 *Cogn Neurosci* 23:2171-2185.

1058 Frazer AK, Williams J, Spittle M, Kidgell DJ (2017) Cross-education of muscular strength is  
1059 facilitated by homeostatic plasticity. *Eur J Appl Physiol* 117:665-677.

1060 Freeland AE, Luber KT (2005) Biomechanics and Biology of Plate Fixation of Distal Radius  
1061 Fractures. *Hand Clin* 21:329-339.

1062 Fuhr P, Agostino R, Hallett M (1991) Spinal motor neuron excitability during the silent period  
1063 after cortical stimulation. *Electroencephalogr Clin Neurophysiol* 81:257-262.

1064 Gabriel DA, Kamen G, Frost G (2006) Neural adaptations to resistive exercise: mechanisms  
1065 and recommendations for training practices. *Sports Med* 36:133-149.

1066 Gandevia SC (2001) Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev*  
1067 81:1725-1789.

1068 Garfinkel S, Cafarelli E (1992) Relative changes in maximal force, EMG, and muscle cross-  
1069 sectional area after isometric training. *Med Sci Sports Exerc* 24:1220-1227.

1070 Garry MI, Loftus A, Summers JJ (2005) Mirror, mirror on the wall: viewing a mirror reflection  
1071 of unilateral hand movements facilitates ipsilateral M1 excitability. *Exp Brain Res*  
1072 163:118-122.

1073 Goodall S, Howatson G, Romer L, Ross E (2014) Transcranial magnetic stimulation in sport  
1074 science: A commentary. *Eur J Sport Sci* 14:S332-S340.

1075 Goodall S, Romer LM, Ross EZ (2009) Voluntary activation of human knee extensors  
1076 measured using transcranial magnetic stimulation. *Exp Physiol* 94:995-1004.

1077 Goodwill AM, Daly RM, Kidgell DJ (2015) The effects of anodal-tDCS on cross-limb transfer  
1078 in older adults. *Clin Neurophysiol* 126:2189-2197.

1079 Goodwill AM, Kidgell DJ (2012) The Effects of Whole-Body Vibration on the Cross-Transfer  
1080 of Strength *The Scientific World Journal* 2012:11.

1081 Goodwill AM, Pearce AJ, Kidgell DJ (2012) Corticomotor plasticity following unilateral  
1082 strength training. *Muscle Nerve* 46:384-393.

1083 Grafton ST, Hazeltine E, Ivry R (1995) Functional Mapping of Sequence Learning in Normal  
1084 Humans. *J Cogn Neurosci* 7:497-510.

1085 Grafton ST, Hazeltine E, Ivry RB (2002) Motor sequence learning with the nondominant left  
1086 hand. *Exp Brain Res* 146:369-378.

1087 Greicius MD, Supekar K, Menon V, Dougherty RF (2009) Resting-State Functional  
1088 Connectivity Reflects Structural Connectivity in the Default Mode Network. *Cereb*  
1089 *Cortex* 19:72-78.

1090 Haller S, Chapuis D, Gassert R, Burdet E, Klarhöfer M (2009) Supplementary motor area and  
1091 anterior intraparietal area integrate fine-graded timing and force control during  
1092 precision grip. *Eur J Neurosci* 30:2401-2406.

1093 Hallett M (2007) Transcranial magnetic stimulation: a primer. *Neuron* 55:187-199.

1094 Hamnegård C-H, Sedler M, Polkey MI, Bake B (2004) Quadriceps strength assessed by  
1095 magnetic stimulation of the femoral nerve in normal subjects. *Clin Physiol Funct*  
1096 *Imaging* 24:276-280.

1097 Hamzei F, Lämpchen CH, Glauche V, Mader I, Rijntjes M, Weiller C (2012) Functional  
1098 Plasticity Induced by Mirror Training: The Mirror as the Element Connecting Both  
1099 Hands to One Hemisphere. *Neurorehabil Neural Repair* 26:484-496.

1100 Hardwick RM, Rottschy C, Miall RC, Eickhoff SB (2013) A quantitative meta-analysis and  
1101 review of motor learning in the human brain. *Neuroimage* 67:283-297.

1102 Harris ML, Luo YM, Watson AC, Rafferty GF, Polkey MI, Green M, Moxham J (2000)  
1103 Adductor Pollicis Twitch Tension Assessed by Magnetic Stimulation of the Ulnar  
1104 Nerve. *Am J Respir Crit Care Med* 162:240-245.

1105 He SQ, Dum RP, Strick PL (1993) Topographic organization of corticospinal projections from  
1106 the frontal lobe: motor areas on the lateral surface of the hemisphere. *J Neurosci* 13:952-  
1107 980.

1108 He SQ, Dum RP, Strick PL (1995) Topographic organization of corticospinal projections from  
1109 the frontal lobe: motor areas on the medial surface of the hemisphere. *J Neurosci*  
1110 15:3284-3306.

1111 Hellebrandt F (1951) Cross Education: Ipsilateral and Contralateral Effects of Unimanual  
1112 Training. *J Appl Physiol* 4:136-144.

1113 Hendy A, Kidgell D (2014) Anodal-tDCS applied during unilateral strength training increases  
1114 strength and corticospinal excitability in the untrained homologous muscle. *Exp Brain*  
1115 *Res* 232:3242-3252.

1116 Hendy AM, Lamon S (2017) The Cross-Education Phenomenon: Brain and Beyond. *Front*  
1117 *Physiol* 8:297.

1118 Hendy AM, Teo W-P, Kidgell DJ (2015) Anodal tDCS Prolongs the Cross-education of  
1119 Strength and Corticomotor Plasticity. *Med Sci Sports Exerc* 47:1788-1797.

1120 Herbert RD, Gandevia SC (1999) Twitch Interpolation in Human Muscles: Mechanisms and  
1121 Implications for Measurement of Voluntary Activation. *J Neurophysiol* 82:2271-2283.

1122 Héroux ME, Taylor JL, Gandevia SC (2015) The use and abuse of transcranial magnetic  
1123 stimulation to modulate corticospinal excitability in humans. *PLOS ONE* 10:e0144151.

1124 Héroux ME, Loo CK, Taylor JL, Gandevia SC (2017) Questionable science and reproducibility  
1125 in electrical brain stimulation research. *PLOS ONE* 12:e0175635.

1126 Heyes C (2010) Where do mirror neurons come from? *Neurosci Biobehav Rev* 34:575-583.

1127 Hortobágyi T et al. (1996) Greater initial adaptations to submaximal muscle lengthening than  
1128 maximal shortening. *J Appl Physiol* 81:1677-1682.

1129 Hortobágyi T, Lambert NJ, Hill JP (1997) Greater cross education following training with  
1130 muscle lengthening than shortening. *Med Sci Sports Exerc* 29:107-112.

1131 Hortobágyi T et al. (2011) Interhemispheric Plasticity in Humans. *Med Sci Sports Exerc*  
1132 43:1188-1199.

1133 Hortobágyi T, Scott K, Lambert J, Hamilton G, Tracy J (1999) Cross-education of muscle  
1134 strength is greater with stimulated than voluntary contractions. *Motor Control* 3:205-  
1135 219.

1136 Hortobágyi T, Taylor JL, Petersen NT, Russell G, Gandevia SC (2003) Changes in Segmental  
1137 and Motor Cortical Output With Contralateral Muscle Contractions and Altered  
1138 Sensory Inputs in Humans. *J Neurophysiol* 90:2451-2459.

1139 Howatson G et al. (2011) Ipsilateral motor cortical responses to TMS during lengthening and  
1140 shortening of the contralateral wrist flexors. *Eur J Neurosci* 33:978-990.

1141 Howatson G, Zult T, Farthing JP, Zijdwind I, Hortobágyi T (2013) Mirror training to augment  
1142 cross-education during resistance training: a hypothesis. *Front Behav Neurosci* 7:396.

1143 Iacoboni M (2005) Neural mechanisms of imitation. *Curr Opin Neurobiol* 15:632-637.

1144 Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G (1999) Cortical  
1145 Mechanisms of Human Imitation. *Sci* 286:2526.

1146 Issurin VB (2005) Vibrations and their applications in sport: a review. *J Sports Med Phys*  
1147 *Fitness* 45:324-336.

1148 Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RS, Passingham RE (1994) Motor sequence  
1149 learning: a study with positron emission tomography. *J Neurosci* 14:3775-3790.

1150 Kannus P et al. (1992) Effect of one-legged exercise on the strength, power and endurance of  
1151 the contralateral leg. *Eur J Appl Physiol* 64:117-126.

1152 Kelly AMC, Garavan H (2005) Human Functional Neuroimaging of Brain Changes Associated  
1153 with Practice. *Cereb Cortex* 15:1089-1102.

1154 Kermadi Y, Liu EM, Rouiller I (2000) Do bimanual motor actions involve the dorsal premotor  
1155 (PMd), cingulate (CMA) and posterior parietal (PPC) cortices? Comparison with  
1156 primary and supplementary motor cortical areas. *Somatosens Mot Res* 17:255-271.

1157 Kidgell D, Goodwill A, Frazer A, Daly R (2013) Induction of cortical plasticity and improved  
1158 motor performance following unilateral and bilateral transcranial direct current  
1159 stimulation of the primary motor cortex. *BMC Neuroscience* 14:64.



1160 Kidgell DJ, Bonanno DR, Frazer AK, Howatson G, Pearce AJ (2017) Corticospinal responses  
1161 following strength training: a systematic review and meta-analysis. *Eur J Neurosci*  
1162 doi:10.1111/ejn.13710.

1163 Kidgell DJ, Frazer AK, Rantalainen T, Ruotsalainen I, Ahtiainen J, Avela J, Howatson G (2015)  
1164 Increased cross-education of muscle strength and reduced corticospinal inhibition  
1165 following eccentric strength training. *Neurosci* 300:566-575.

1166 Kidgell DJ, Pearce AJ (2010) Corticospinal properties following short-term strength training  
1167 of an intrinsic hand muscle. *Hum Mov Sci* 29:631-641.

1168 Kidgell DJ, Stokes MA, Castricum TJ, Pearce AJ (2010) Neurophysiological Responses After  
1169 Short-Term Strength Training of the Biceps Brachii Muscle. *J Strength Cond Res*  
1170 24:3123-3132.

1171 Kidgell DJ, Stokes MA, Pearce AJ (2011) Strength Training of One Limb Increases  
1172 Corticomotor Excitability Projecting to the Contralateral Homologous Limb. *Motor*  
1173 *Control* 15:247-266.

1174 Kim C-Y, Lee J-S, Kim H-D, Kim J-S (2015) The effect of progressive task-oriented training  
1175 on a supplementary tilt table on lower extremity muscle strength and gait recovery in  
1176 patients with hemiplegic stroke. *Gait Posture* 41:425-430.

1177 Kobayashi M, Hutchinson S, Schlaug G, Pascual-Leone A (2003) Ipsilateral motor cortex  
1178 activation on functional magnetic resonance imaging during unilateral hand movements  
1179 is related to interhemispheric interactions. *Neuroimage* 20:2259-2270.

1180 Koeneke S, Lutz K, Wüstenberg T, Jäncke L (2004) Bimanual versus unimanual coordination:  
1181 what makes the difference? *Neuroimage* 22:1336-1350.

1182 Kremenic IJ, Ben-Avi SS, Leonhardt D, McHugh MP (2004) Transcutaneous magnetic  
1183 stimulation of the quadriceps via the femoral nerve. *Muscle Nerve* 30:379-381.

1184 Kujirai T et al. (1993) Corticocortical inhibition in human motor cortex. *J Physiol* 471:501-  
1185 519.

1186 Lagerquist O, Zehr EP, Docherty D (2006) Increased spinal reflex excitability is not associated  
1187 with neural plasticity underlying the cross-education effect. *J Appl Physiol* 100:83-90.

1188 Lampropoulou SI, Nowicky AV, Marston L (2012) Magnetic Versus Electrical Stimulation in  
1189 the Interpolation Twitch Technique of Elbow Flexors. *J Sports Sci Med* 11:709-718.

1190 Lang N et al. (2005) How does transcranial DC stimulation of the primary motor cortex alter  
1191 regional neuronal activity in the human brain? *Eur J Neurosci* 22:495-504.

1192 Lapole T, Canon F, Pérot C (2013) Ipsi- and contralateral H-reflexes and V-waves after  
1193 unilateral chronic Achilles tendon vibration. *Eur J Appl Physiol*:1-9.

1194 Lämpchen CH, Ringer T, Blessin J, Seidel G, Grieshammer S, Lange R, Hamzei F (2012)  
1195 Optical illusion alters M1 excitability after mirror therapy: a TMS study. *J*  
1196 *Neurophysiol* 108:2857-2861.

1197 Latella C, Kidgell D, Pearce A (2012) Reduction in corticospinal inhibition in the trained and  
1198 untrained limb following unilateral leg strength training. *Eur J Appl Physiol* 112:3097-  
1199 3107.

1200 Lee M, Gandevia SC, Carroll TJ (2008) Cortical voluntary activation can be reliably measured  
1201 in human wrist extensors using transcranial magnetic stimulation. *Clin Neurophysiol*  
1202 119:1130-1138.

1203 Lee M, Gandevia SC, Carroll T (2009a) Short-term strength training does not change cortical  
1204 voluntary activation. *Med Sci Sports Exerc* 41:1452-1460.

1205 Lee M, Gandevia SC, Carroll TJ (2009b) Unilateral strength training increases voluntary  
1206 activation of the opposite untrained limb. *Clin Neurophysiol* 120:802-808.

1207 Lee M, Hinder MR, Gandevia SC, Carroll TJ (2010) The ipsilateral motor cortex contributes  
1208 to cross-limb transfer of performance gains after ballistic motor practice. *J Physiol*  
1209 588:201-212.

1210 Legrand D, Vaes B, Matheï C, Adriaensen W, Van Pottelbergh G, Degryse JM (2014) Muscle  
1211 strength and physical performance as predictors of mortality, hospitalization, and  
1212 disability in the oldest old. *J Am Geriatr Soc* 62:1030-1038.

1213 Lepley LK, Palmieri-Smith RM (2014) Cross-Education Strength and Activation After  
1214 Eccentric Exercise. *J Athl Train* 49:582-589.

1215 Leung M, Rantalainen T, Teo W-P, Kidgell D (2017) The corticospinal responses of  
1216 metronome-paced, but not self-paced strength training are similar to motor skill training.  
1217 *Eur J Appl Physiol* 117:2479-2492.

1218 Lin VWH, Deng X, Lee YS, Hsiao IN (2008) Stimulation of the Expiratory Muscles Using  
1219 Microstimulators. *IEEE Trans Neural Syst Rehabil Eng* 16:416-420.

1220 Logothetis NK (2003) MR imaging in the non-human primate: studies of function and of  
1221 dynamic connectivity. *Curr Opin Neurobiol* 13:630-642.

1222 Magnus CRA, Arnold CM, Johnston G, Dal-Bello Haas V, Basran J, Krentz JR, Farthing JP  
1223 (2013) Cross-education for improving strength and mobility following distal radius  
1224 fractures: A preliminary randomized controlled trial. *Arch Phys Med Rehabil* 94:1247-  
1225 1255.

1226 Manca A et al. (2015) A comprehensive assessment of the cross-training effect in ankle  
1227 dorsiflexors of healthy subjects: A randomized controlled study. *Gait Posture* 42:1-6.

1228 Manca A et al. (2016a) No evidence of neural adaptations following chronic unilateral  
1229 isometric training of the intrinsic muscles of the hand: a randomized controlled study.  
1230 *Eur J Appl Physiol* 116:1993-2005.

1231 Manca A et al. (2016b) Effect of Contralateral Strength Training on Muscle Weakness in  
1232 People With Multiple Sclerosis: Proof-of-Concept Case Series. *Phys Ther* 96:828-838.

1233 Manca A, Dragone D, Dvir Z, Deriu F (2017a) Cross-education of muscular strength following  
1234 unilateral resistance training: a meta-analysis. *Eur J Appl Physiol* 117:2335-2354.

1235 Manca A et al. (2017b) Resistance Training for Muscle Weakness in Multiple Sclerosis: Direct  
1236 Versus Contralateral Approach in Individuals With Ankle Dorsiflexors' Disparity in  
1237 Strength. *Arch Phys Med Rehabil* 98:1348-1356.

1238 Martin A, Haxby JV, Lalonde FM, Wiggs CL, Ungerleider LG (1995) Discrete Cortical  
1239 Regions Associated with Knowledge of Color and Knowledge of Action. *Sci* 270:102.

1240 Mason J, Frazer AK, Horvath DM, Pearce AJ, Avela J, Howatson G, Kidgell DJ (2017a)  
1241 Ipsilateral corticomotor responses are confined to the homologous muscle following  
1242 cross-education of muscular strength. *Appl Physiol Nutr Metab* 43:11-22.

1243 Mason J, Frazer A, Horvath DM, Pearce AJ, Avela J, Howatson G, Kidgell D (2017b)  
1244 Adaptations in corticospinal excitability and inhibition are not spatially confined to the  
1245 agonist muscle following strength training. *Eur J Appl Physiol* 117:1359-1371.

1246 Matsumoto L, Hanajima R, Matsumoto H, Ohminami S, Terao Y, Tsuji S, Ugawa Y (2010)  
1247 Supramaximal responses can be elicited in hand muscles by magnetic stimulation of  
1248 the cervical motor roots. *Brain Stimulation: Basic, Translational, and Clinical Research*  
1249 *in Neuromodulation* 3:153-160.

1250 Matthys K, Smits M, Van der Geest JN, Van der Lugt A, Seurinck R, Stam HJ, Selles RW  
1251 (2009) Mirror-Induced Visual Illusion of Hand Movements: A Functional Magnetic  
1252 Resonance Imaging Study. *Arch Phys Med Rehabil* 90:675-681.

1253 Mazzocchio R, Rothwell JC, Day BL, Thompson PD (1994) Effect of tonic voluntary activity  
1254 on the excitability of human motor cortex. *J Physiol* 474:261-267.

1255 McKay S, MacDermid J, Roth J, Richards R (2001) Assessment of complications of distal radius  
1256 fractures and development of a complication checklist. *J Hand Surg* 26:916-922.

1257 Merton PA (1954) Voluntary strength and fatigue. *J Physiol* 123:553-564.

1258 Meyers CR (1966) Effects of two isometric routines on strength size and endurance in  
1259 exercised and non-exercised arms. *Res Quart* 38:430-440.

1260 Millet GY, Martin V, Martin A, Vergès S (2011) Electrical stimulation for testing  
1261 neuromuscular function: from sport to pathology. *Eur J Appl Physiol* 111:2489-2500.

1262 Molenaar JP, McNeil CJ, Bredius MS, Gandevia SC (2013) Effects of aging and sex on  
1263 voluntary activation and peak relaxation rate of human elbow flexors studied with  
1264 motor cortical stimulation. *AGE* 35:1327-1337.

1265 Moreland JD, Richardson JA, Goldsmith CH, Clase CM (2004) Muscle weakness and falls in  
1266 older adults: A systematic review and meta-analysis. *J Am Geriatr Soc* 52:1121-1129.

1267 Munn J, Herbert RD, Gandevia SC (2004) Contralateral effects of unilateral resistance training:  
1268 a meta-analysis. *J Appl Physiol* 96:1861-1866.

1269 Munn J, Herbert RD, Hancock MJ, Gandevia SC (2005) Training with unilateral resistance  
1270 exercise increases contralateral strength. *J Appl Physiol* 99:1880-1884.

1271 Nielsen J, Petersen N (1995) Changes in the effect of magnetic brain stimulation accompanying  
1272 voluntary dynamic contraction in man. *J Physiol* 484:777-789.

1273 Nitsche MA et al. (2008) Transcranial direct current stimulation: State of the art 2008. *Brain*  
1274 *Stim* 1:206-223.

1275 Nojima I, Mima T, Koganemaru S, Thabit MN, Fukuyama H, Kawamata T (2012) Human  
1276 Motor Plasticity Induced by Mirror Visual Feedback. *J Neurosci* 32:1293.

1277 Nordlund MM, Thorstensson A (2007) Strength training effects of whole-body vibration?  
1278 *Scand J Med Sci Sports* 17:12-17.

1279 Nuzzo JL, Barry BK, Jones MD, Gandevia SC, Taylor JL (2017) Effects of four weeks of  
1280 strength training on the corticomotoneuronal pathway. *Med Sci Sports Exerc* 49: 2286-  
1281 2296.

1282 Oakman A, Zhou S, Davie A (1999) Cross-education effect observed in voluntary  
1283 electromyostimulation strength training. In: Sanders RH, Gibson BJ (eds) *Proceedings*  
1284 *of the XVII International Symposium of Biomechanics in Sports*. Perth, Australia, pp  
1285 401-404.

1286 Obayashi S (2004) Possible mechanism for transfer of motor skill learning: implication of the  
1287 cerebellum. *Cerebellum* 3:204-211.

1288 Olney RK, So YT, Goodin DS, Aminoff MJ (1990) A comparison of magnetic and electrical  
1289 stimulation of peripheral nerves. *Muscle Nerve* 13:957-963.

1290 Palmer HS et al. (2013) Structural brain changes after 4 wk of unilateral strength training of  
1291 the lower limb. *J Appl Physiol* 115:167-175.

1292 Papandreou M, Billis E, Papathanasiou G, Spyropoulos P, Papaioannou N (2013) Cross-  
1293 Exercise on Quadriceps Deficit after ACL Reconstruction. *J Knee Surg* 26:51-58.

1294 Pearce AJ, Hendy A, Bowen WA, Kidgell DJ (2012) Corticospinal adaptations and strength  
1295 maintenance in the immobilized arm following 3 weeks unilateral strength training.  
1296 *Scand J Med Sci Sports* 23:740-748.

1297 Perez MA, Cohen LG (2008) Mechanisms Underlying Functional Changes in the Primary  
1298 Motor Cortex Ipsilateral to an Active Hand. *J Neurosci* 28:5631-5640.

1299 Perez MA, Cohen LG (2009) Interhemispheric inhibition between primary motor cortices:  
1300 what have we learned? *J Physiol* 587:725-726.

1301 Perez MA, Lundbye-Jensen J, Nielsen JB (2007a) Task-Specific Depression of the Soleus H-  
1302 Reflex After Cocontraction Training of Antagonistic Ankle Muscles. *J Neurophysiol*  
1303 98:3677-3687.

1304 Perez MA, Tanaka S, Wise SP, Sadato N, Tanabe HC, Willingham DT, Cohen LG (2007b)  
1305 Neural Substrates of Intermanual Transfer of a Newly Acquired Motor Skill. *Curr Biol*  
1306 17:1896-1902.

1307 Perez MA, Wise SP, Willingham DT, Cohen LG (2007c) Neurophysiological Mechanisms  
1308 Involved in Transfer of Procedural Knowledge. *J Neurosci* 27:1045-1053.

1309 Porter R (1985) The corticomotoneuronal component of the pyramidal tract:  
1310 corticomotoneuronal connections and functions in primates. *Brain Res* 357:1-26.

1311 Ramachandran V, Rogers-Ramachandran D (1996) Synaesthesia in phantom limbs induced  
1312 with mirrors. *Proc R Soc Lond B Biol Sci* 263:377.

1313 Ray E, Heyes C (2011) Imitation in infancy: the wealth of the stimulus. *Dev Sci* 14:92-105.

1314 Reynolds C, Ashby P (1999) Inhibition in the human motor cortex is reduced just before a  
1315 voluntary contraction. *Neurol* 53:730.

1316 Ridding MC, Taylor JL, Rothwell JC (1995) The effect of voluntary contraction on cortico-  
1317 cortical inhibition in human motor cortex. *J Physiol* 487:541-548.

1318 Rittweger J (2010) Vibration as an exercise modality: how it may work, and what its potential  
1319 might be. *Eur J Appl Physiol* 108:877-904.

1320 Rittweger J, Mutschelknauss M, Felsenberg D (2003) Acute changes in neuromuscular  
1321 excitability after exhaustive whole body vibration exercise as compared to exhaustion  
1322 by squatting exercise. *Clin Physiol Funct Imaging* 23:81-86.

1323 Rizzolatti G, Craighero L (2004) The Mirror-Neuron System. *Annu Rev Neurosci* 27:169-192.

1324 Rizzolatti G, Fadiga L, Fogassi L, Gallese V (1999) Resonance Behaviors and Mirror Neurons.  
1325 *Arch Ital Biol* 137:85-100.

1326 Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D, Fazio F (1996)  
1327 Localization of grasp representations in humans by PET: 1. Observation versus  
1328 execution. *Exp Brain Res* 111:246-252.

1329 Ross EZ, Middleton N, Shave R, George K, Nowicky A (2007) Corticomotor excitability  
1330 contributes to neuromuscular fatigue following marathon running in man. *Exp Physiol*  
1331 92:417-426.

1332 Rossini PM, Rossi S (2007) Transcranial magnetic stimulation: diagnostic, therapeutic, and  
1333 research potential. *Neurol* 68:484-488.

1334 Rothwell JC, Day BL, Thompson PD, Kujirai T (2009) Short latency intracortical inhibition:  
1335 one of the most popular tools in human motor neurophysiology. *J Physiol* 587:11-12.

1336 Ruddy KL, Carson RG (2013) Neural pathways mediating cross education of motor function.  
1337 *Front Hum Neurosci* 7:397.

1338 Ruddy KL, Leemans A, Woolley DG, Wenderoth N, Carson RG (2017) Structural and  
1339 Functional Cortical Connectivity Mediating Cross Education of Motor Function. *J*  
1340 *Neurosci* 37:2555-2564.

1341 Ruddy KL, Rudolf AK, Kalkman B, King M, Daffertshofer A, Carroll TJ, Carson RG (2016)  
1342 Neural Adaptations Associated with Interlimb Transfer in a Ballistic Wrist Flexion  
1343 Task. *Front Hu Neurosci* 10:204.

1344 Sakadjian A, Panchuk D, Pearce AJ (2014) Kinematic and Kinetic Improvements Associated  
1345 With Action Observation Facilitated Learning of the Power Clean in Australian  
1346 Footballers. *J Strength Cond Res* 28:1613-1625.

1347 Schubotz RI, von Cramon DY (2002) A Blueprint for Target Motion: fMRI Reveals Perceived  
1348 Sequential Complexity to Modulate Premotor Cortex. *Neuroimage* 16:920-935.

1349 Scripture EW, Smith TL, Brown EM (1894) On the education of muscular control and power.  
1350 *Studies Yale Psychol Lab* 2:114-119.

1351 Shaver L (1970) Effects of training on relative muscular endurance in ipsilateral and  
1352 contralateral arms. *Med Sci Sports* 2:172-175.



- 1353 Shaver LG (1975) Cross transfer effect of conditioning and deconditioning on muscular  
1354 strength. *Ergonomics* 18:9-16.
- 1355 Shield A, Shi Z (2004) Assessing Voluntary Muscle Activation with the Twitch Interpolation  
1356 Technique. *Sports Med* 34:253-267.
- 1357 Shima N, Ishida K, Katayama K, Morotome Y, Sato Y, Miyamura M (2002) Cross education  
1358 of muscular strength during unilateral resistance training and detraining. *Eur J Appl*  
1359 *Physiol* 86:287-294.
- 1360 Sidhu SK, Bentley DJ, Carroll TJ (2009) Locomotor exercise induces long-lasting impairments  
1361 in the capacity of the human motor cortex to voluntarily activate knee extensor muscles.  
1362 *J Appl Physiol* 106:556-565.
- 1363 Small SL, Buccino G, Solodkin A (2012) The mirror neuron system and treatment of stroke.  
1364 *Dev Psychobiol* 54:293-310.
- 1365 Spink MJ, Fotoohabadi MR, Wee E, Hill KD, Lord SR, Menz HB (2011) Foot and ankle  
1366 strength, range of motion, posture, and deformity are associated with balance and  
1367 functional ability in older adults. *Arch of Phys Med Rehabil* 92:68-75.
- 1368 Sütbeyaz S, Yavuzer G, Sezer N, Koseoglu BF (2007) Mirror Therapy Enhances Lower-  
1369 Extremity Motor Recovery and Motor Functioning After Stroke: A Randomized  
1370 Controlled Trial. *Arch Phys Med Rehabil* 88:555-559.
- 1371 Suzuki T, Bean Jonathan F, Fielding Roger A (2002) Muscle power of the ankle flexors  
1372 predicts functional performance in community-dwelling older women. *J Am Geriatr*  
1373 *Soc* 49:1161-1167.
- 1374 Taylor JL, Martin PG (2009) Voluntary motor output is altered by spike-timing-dependent  
1375 changes in the human corticospinal pathway. *J Neurosci* 29:11708.

1376 Thickbroom GW, Phillips BA, Morris I, Byrnes ML, Sacco P, Mastaglia FL (1999) Differences  
1377 in functional magnetic resonance imaging of sensorimotor cortex during static and  
1378 dynamic finger flexion. *Exp Brain Res* 126:431-438.

1379 Todd G, Taylor JL, Gandevia SC (2004) Reproducible measurement of voluntary activation of  
1380 human elbow flexors with motor cortical stimulation. *J Appl Physiol* 97:236-242.

1381 Todd G, Taylor JL, Gandevia SC (2016) Measurement of voluntary activation based on  
1382 transcranial magnetic stimulation over the motor cortex. *J Appl Physiol* 121:678-686.

1383 Tøien T, Unhjem R, Øren TS, Kvellestad ACG, Hoff J, Wang E (2017) Neural Plasticity with  
1384 Age: Unilateral Maximal Strength Training Augments Efferent Neural Drive to the  
1385 Contralateral Limb in Older Adults. *J Gerontol: Series A*.

1386 Tomazin K, Verges S, Decorte N, Oulerich A, Maffiuletti NA, Millet GY (2011) Fat tissue  
1387 alters quadriceps response to femoral nerve magnetic stimulation. *Clin Neurophysiol*  
1388 122:842-847.

1389 Tomazin K, Verges S, Decorte N, Oulerich A, Millet GY (2010) Effects of coil characteristics  
1390 for femoral nerve magnetic stimulation. *Muscle Nerve* 41:406-409.

1391 Ugawa Y, Terao Y, Hanajima R, Sakai K, Kanazawa I (1995) Facilitatory effect of tonic  
1392 voluntary contraction on responses to motor cortex stimulation *Electroencephalo Clin*  
1393 *Neurophysiol* 97:451-454.

1394 Valls-Solé J, Pascual-Leone A, Wassermann EM, Hallett M (1992) Human motor evoked  
1395 responses to paired transcranial magnetic stimuli. *Electroencephalography and Clin*  
1396 *Neurophysiol/Evoked Potentials Sec* 85:355-364.

1397 Vivodtzev I, Wuyam B, Flore P, Lévy P (2005) Changes in quadriceps twitch tension in  
1398 response to resistance training in healthy sedentary subjects. *Muscle Nerve* 32:326-334.

1399 Weier AT, Pearce AJ, Kidgell DJ (2012) Strength Training Reduces Intracortical Inhibition  
1400 *Acta Physiologica* 206:109-119.

1401 Weir JP, Housh DJ, Housh TJ, Weir LL (1995) The Effect of Unilateral Eccentric Weight  
1402 Training and Detraining on Joint Angle Specificity, Cross-Training, and the Bilateral  
1403 Deficit. *J Orthop Sports Phys Ther* 22:207-215.

1404 Weir JP, Housh DJ, Housh TJ, Weir LL (1997) The Effect of Unilateral Concentric Weight  
1405 Training and Detraining on Joint Angle Specificity, Cross-Training, and the Bilateral  
1406 Deficit. *J Orthop Sports Phys Ther* 25:264-270.

1407 Werhahn KJ, Classen J, Benecke R (1995) The silent period induced by transcranial magnetic  
1408 stimulation in muscles supplied by cranial nerves: normal data and changes in patients.  
1409 *J Neurol Neurosurg Psychiatry* 59:586-596.

1410 Wilson SA, Lockwood RJ, Thickbroom GW, Mastaglia FL (1993) The muscle silent period  
1411 following transcranial magnetic cortical stimulation. *J Neurol Sci* 114:216-222.

1412 Winterer G, Adams CM, Jones DW, Knutson B (2002) Volition to Action—An Event-Related  
1413 fMRI Study. *Neuroimage* 17:851-858.

1414 Xiong J, Ma L, Wang B, Narayana S, Duff EP, Egan GF, Fox PT (2009) Long-term motor  
1415 training induced changes in regional cerebral blood flow in both task and resting states.  
1416 *Neuroimage* 45:75-82.

1417 Yavuzer G et al. (2008) Mirror Therapy Improves Hand Function in Subacute Stroke: A  
1418 Randomized Controlled Trial. *Arch Phys Med Rehabil* 89:393-398.

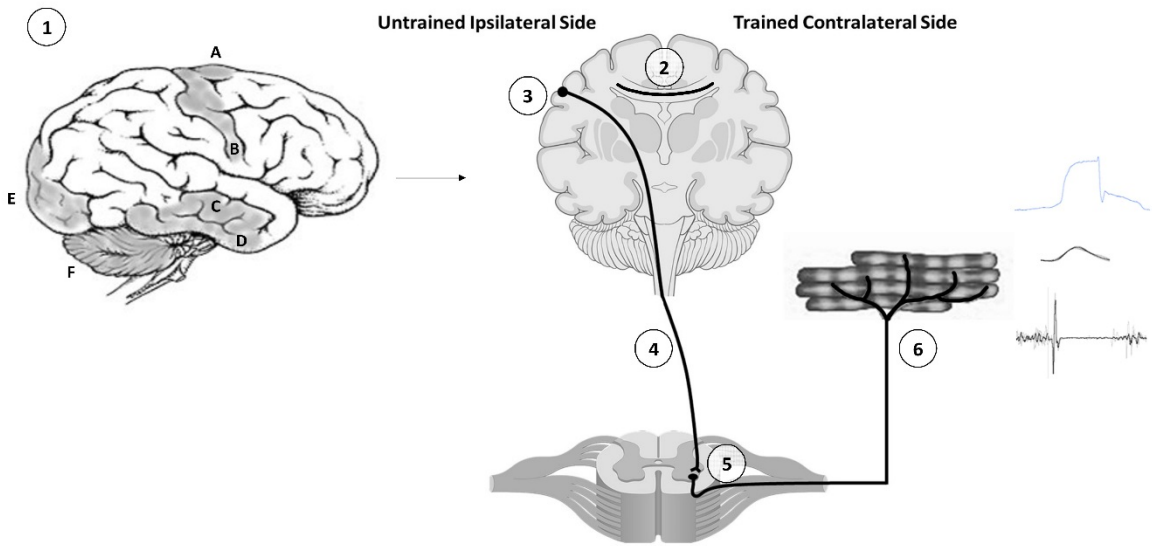
1419 Yue G, Cole KJ (1992) Strength increases from the motor program: comparison of training  
1420 with maximal voluntary and imagined muscle contractions. *J Neurophysiol* 67:1114-  
1421 1123.

1422 Zult T, Goodall S, Thomas K, Hortobagyi T, Howatson G (2015) Mirror illusion reduces motor  
1423 cortical inhibition in the ipsilateral primary motor cortex during forceful unilateral  
1424 muscle contractions. *J Neurophysiol* 113:2262-2270.

- 1425 Zult T, Goodall S, Thomas K, Solnik S, Hortobágyi T, Howatson G (2016) Mirror Training  
1426 Augments the Cross-education of Strength and Affects Inhibitory Paths. Med Sci Sports  
1427 Exerc 48:1001-1013.
- 1428 Zult T, Howatson G, Kádár E, Farthing J, Hortobágyi T (2014) Role of the Mirror-Neuron  
1429 System in Cross-Education. Sports Med 44:1-20.
- 1430

1431 **Figure 1.** Potential sites of neural adaptation to cross education include **(1)** changes in (A)  
1432 supplementary motor area, (B) primary motor cortex, (C) middle temporal gyrus, (D) inferior  
1433 temporal gyrus, (E) occipital lobe, (F) cerebellum, **(2)** changes in interhemispheric inhibition,  
1434 **(3)** changes in TMS measures confined to the ipsilateral “untrained” primary motor cortex  
1435 (SICI), **(4)** changes along the corticospinal tract ipsilateral to the trained limb (excitability and  
1436 inhibition), **(5)** changes in motoneurone excitability, and **(6)** changes in  $VA_{TMS}$ , raw EMG  
1437 response (MEP) produced by cortical stimulation during maximal contraction, as well as the  
1438 superimposed twitch produced by cortical stimulation during maximal contraction, (right).

1439



1440

1441 **Table 1:** Summary of studies examining the effect of unilateral motor-training on structural connectivity and patterns of brain activation.

1442

Study	Subject Details	Muscle Group	Methods	Training Details	Training Intensity	Strength Gain	Results
Ruddy et al. 2017	44 subjects (20 control, 24 experimental)	Wrist flexors	rs-fMRI and DWI	One session	300 'fast as possible' wrist flexion	↑ 83% peak acceleration	↑rs-fMRI of right/left SMA; DWI was associated with increased transfer
Farthing et al. 2007	23 subjects (12 physical training, 11 imagery)	Flexor Carpi Ulnaris	fMRI patterns of activation, maximal isometric muscle activation (EMG)	6 wks of unilateral isometric training	Isometric MVC 6 × 8 reps	↑ 47.1% MVC	↑ muscle activation ↑ activation M1 and SMA, left ventral M1 and SMA, left anterior and posterior middle temporal gyrus, left inferior temporal gyrus, medial occipital cortex and posterior medial and lateral cerebellum

1456 **DWI:** diffusion weighted imaging; **EMG:** electromyography; **M1:** motor cortex; **MVC:** maximum voluntary contraction; **rs-fMRI:** resting-state functional magnetic  
 1457 resonance imaging; **SMA:** supplementary motor area; **wks:** weeks

1458

1459 **Table 2:** Summary of studies examining the effect of cross-education training on cortical excitability and inhibition.

1460

Study	Participant Details	Muscle Group	Training Details	TMS Method	TMS Outcome for untrained limb
Hortobágyi et al. 2011	20 participants (12 trained, 8 control)	First dorsal interosseous	5 × 10 MVCs performed at 80%, 3/wk × 8 wks	MEPs, SICI, ICF & IHI during 20 and 80% MVC	↑ MEPs at 20 and 80% MVC, ↓IHI
Kidgell et al. 2011	26 participants (13 trained, 13 control)	Biceps brachii	4 × 6-8 bicep curls at 80% 1-RM, 3/wk × 4 wks	MEPs and CSP during 10% <i>rms</i> EMG	↑ MEPs during, ↔ CSP
Latella et al. 2012	18 participants (9 trained, 9 control)	Rectus Femoris	3 × 8 leg presses at 78%-88.5% 1-RM, 3/wk × 8 wks	MEPs and CSP during 10% <i>rms</i> EMG	↔ MEPs during 10% <i>rms</i> EMG, ↓CSP
Goodwill et al. 2012	14 participants (7 trained, 7 control)	Rectus Femoris	4 × 8 single-leg squats at 80% 1-RM, 3/wk × 4 wks	MEPS and SICI during 10% MVC	↑ MEP <sub>max</sub> , ↓SICI
Kidgell et al. 2015 (concentric)	18 participants (9 trained, 9 control)	Wrist flexors	4 × 8 maximal concentric wrist flexion performed at 20°/s	MEPs, SICI and CSP during 5, 20 and 40% MVC and 40%	↔MEPs at 5, 20 & 40% MVC, ↔SICI at 5, 20 & 40% MVC, ↔CSP at 5, 20 & 40% MVC
Kidgell et al. 2015 (eccentric)	18 participants (9 trained, 9 control)	Wrist flexors	4 × 8 maximal eccentric wrist flexion performed at 20°/s	MEPs, SICI and CSP during 5, 20 and 40% MVC and 40%	↑MEPs at 40% MVC, ↓SICI at 40% MVC, ↓CSP at 5 & 20% MVC
Coombs et al. 2016 (right-hand)	15 participants (8 trained, 7 control)	Wrist extensors	4 × 6-8 wrist extensions at 70% 1-RM for the right arm only	MEPs, SICI and CSP during 5% <i>rms</i> EMG	↔MEPs, ↔SICI, ↓CSP at MEP <sub>max</sub>
Coombs et al. 2016 (left arm)	15 participants (8 trained, 7 control)	Wrist extensors	4 × 6-8 wrist extensions at 70% 1-RM for the left arm only	MEPs, SICI and CSP during 5% <i>rms</i> EMG	↔MEPs, ↔SICI, ↔CSP
Manca et al. 2016a	24 subjects (17 trained, 17 control)	First dorsal interosseous	5 × 10 isometric pinch contractions, 3/wk × 4 wks	MEPs at rest and during 10% MVC, SICI, ICF, SICF, SIHI and LICI	↔MEPs, ↔SICF, ↔SICI, ↔ICF, ↔LICI, ↔SIHI and ↔ LIHI
Mason et al. 2017b	20 participants (10 trained, 10 control)	Biceps brachii	4 × 6-8 bicep curls at 80% 1-RM, 3/wk × 3 wks	MEPs and CSP during 5% <i>rms</i> EMG	↑MEPs and ↓CSP

1461 **1-RM:** one-repetition maximum; **CSP:** cortical silent period; **ICF:** intracortical inhibition; **IHI:** interhemispheric inhibition; **LICF:** long-interval intracortical facilitation; **LICI:**  
 1462 long-interval intracortical inhibition; **MEP:** motor evoked potential; **MVC:** maximum voluntary contraction; **SICF:** short-interval intracortical facilitation; **SICI:** short-interval  
 1463 intracortical inhibition, **wk:** week; **wks:** weeks



1464 **Table 3:** Summary of studies examining the effect of cross-education training on voluntary activation of the untrained limb.

1465

Study	Participant Details	Muscle Group	Training Details	Twitch Method	Twitch Outcome
Lee et al. 2009b	20 participants (10 trained, 10 control)	Wrist extensors	4 × 10 brief (1-2 s) isometric wrist extension, 3/wk × 4 wks	TMS cortical voluntary activation	↓ superimposed twitch evoked during extension MVC
Shima et al. 2002	15 participants (9 trained, 6 control)	Gastrocnemius	3 × 10-12 reps at 70-75% 1-RM, 4/wk × 6 wks	Interpolated twitch technique	↔ voluntary activation
Tøien et al. 2017	23 participants (11 trained, 12 control)	Gastrocnemius	4 × 4 reps at 90% 1-RM, 3/wk × 3 wks	Interpolated twitch technique	↑ voluntary activation
Fimland et al. 2009	26 participants (15 trained, 11 control)	Gastrocnemius	7 × 1 min isometric contractions at 30% MVC, increasing to 15 sets of 1 min, 7/wk × 8 wks	Maximal twitch tension	↔ twitch force

1466 **1-RM:** one-repetition maximum; **MVC:** maximum voluntary contraction; **TMS:** transcranial magnetic stimulation; **wk:** week; **wks:** weeks