Inter-limb mechanisms and clinical relevance of cross-education in humans
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Chapter 1

General introduction
1.1 Introduction and historical perspective

Cross-education, i.e., the performance improvement of the untrained limb after a period of unilateral practice with the homologous contralateral limb, has been known for over 150 years [1]. Initial cross-education research focused on psychomotor tasks like hand writing [1], mirror drawing [2], target hitting [3,4], target hitting while viewing the target in a mirror [5], and finger tapping [3]. In the late 19th century, it became evident that cross-education not only worked for low force motor tasks requiring high skill but also for slow and monotonic resistance exercises [3,4]. Initially, cross-education was the domain of psychology with gains in skill and voluntary muscle force attributed to will-power and the ability to pay attention [3,6]. Subsequently, cross-education became a physiological phenomenon [7,8] with a different neural explanation for improvements in motor skill and muscle force [9]. The remainder of this thesis will primarily focus on unilateral resistance training, including the underlying mechanisms and clinical potential of cross-education. Almost every cross-education study recommended the inclusion of unilateral resistance training on the uninjured side in the rehabilitation from unilateral injury or neurological dysfunction. However, the cross-education effect is only about 8% of initial muscle force [10,11] and the presumed clinical benefits remain largely unexplored and unexploited. For cross-education research to develop, a better understanding of the mechanisms, augmentation, and clinical relevance of cross-education is needed.

1.2 Scope of cross-education

The cross-education of voluntary muscle force has been examined in leg muscles, e.g., knee extensors, as well as in arm and intrinsic hand muscles, like elbow flexors and the first dorsal interosseous [11]. The duration of the unilateral training program is on average 4-12 weeks and exercises are performed at 60-100% of maximal voluntary contraction (MVC) [12]. The magnitude of cross-education is related to the strength increase of the trained muscles [12], with the inter-limb transfer being about 52% of the force gained on the trained side [10]. Cross-education is muscle and contraction specific. Muscle specificity is demonstrated by the greater amount of cross-education for the contralateral homologous than non-homologous muscles [13]. Contraction specificity is illustrated by the higher magnitude of cross-education for the trained contraction mode than the non-trained contraction modes [14].

It is assumed that the transfer is asymmetrical, meaning that the amount of transfer is greater when the dominant than non-dominant
limb is trained. The asymmetrical transfer has been observed for motor skills [15] and muscle force [16]. The idea is that more information can be transferred from the dominant to non-dominant limb because the dominant limb is more proficient at learning novel tasks [15,17]. This unidirectional transfer implicates that the cross-education of muscle force can only be applied in clinical settings where the non-dominant leg needs rehabilitation. However, studies in stroke and wrist fracture patients show that unilateral resistance training induces cross-education, irrespective of whether the dominant or non-dominant limb was trained [18,19]. It can be argued that the more proficient limb becomes the unaffected limb during unilateral dysfunction, and therefore the transfer is present regardless of handedness [17]. Also, a recent study in healthy adults revealed that the cross-education of muscle force was not limited by which limb was trained [20], indicating that the transfer of muscle force is less asymmetrical than previously thought.

Cross-education has been observed in males and females of which the majority had minimal experience in resistance training [12]. Although males are stronger and gain more absolute muscle force than females following unilateral resistance training, the percentage force increase in the trained and contralateral untrained muscles was similar between sexes [21]. Age is also not a limiting factor for inducing cross-education. Most cross-education studies are performed in young adults but also elderly show cross-education [21]. Elderly produce less voluntary muscle force than young adults but the absolute force increase in the trained and contralateral untrained muscles was similar between age groups [22]. The percent change data even suggest, although not statistically tested, that elderly respond better to unilateral resistance training than young adults with 52 vs. 31% force increase on the trained side and 39 vs. 24% cross-education [22]. The broad scope hypothetically makes cross-education a useful tool in the recovery from unilateral dysfunction but definite evidence should be provided by randomized clinical trials.

1.3 Possible mechanisms of cross-education

Cross-education moved from the psychology to physiology domain after the observation that forceful single-handed contractions resulted in concurrent activation of hand muscles on the contralateral resting side [7,8]. The magnitude of this ‘associated activity’ can reach 20% of MVC [14,23,24] and there is proof that resistance training at 10% MVC can improve muscle force [25]. The origin of this ‘associated activity’ following a unilaterally intended motor command is likely the primary motor cortex (M1) ipsilateral to the contracting hand [24]. Indeed, corticospinal
output from the ipsilateral M1 to the resting hand reflects the output of the contralateral M1 to the contracting hand, meaning that the corticospinal output from the ipsilateral M1 increases with increasing contraction intensity [26,27]. The repeated activation of the ipsilateral M1 over multiple unilateral training sessions is assumed to contribute to the cross-education of muscle force [28]. Therefore, unilateral contraction studies are of value in understanding the underlying mechanisms of cross-education.

It is known that the improvement in maximal voluntary force following resistance training is predominantly attributed to neural adaptations in the early training phase with hypertrophy becoming evident after three to five weeks [29]. Hypertrophy was observed in the trained muscles but not in the untrained contralateral muscles after eight weeks of unilateral resistance training [29], suggesting that only neural factors play a role in cross-education. Neural factors could be a more synchronized and increased discharge rate of motor units, reduced antagonist muscle activity, and adaptations in the primary motor cortex [30-32]. Although spinal and supraspinal networks have been mentioned as sources for cross-education, the precise mechanisms are poorly understood [33].

Only a few studies examined the spinal mechanisms related to cross-education. A cross-sectional study showed that muscle stretch superimposed upon a contracting muscle facilitated the force production of the stretched muscle and inhibited the force production of the contralateral homologous muscle, i.e., crossed extensor reflex [34]. Multiple training sessions increased the spinal reflex excitability of the trained muscle but did not change the reflex excitability of the muscle that showed cross-education [35,36]. However, there was a bilateral decrease in reflex excitability of the antagonist muscle [35], indicating that spinal adaptations play a subtle role in the cross-education of muscle force.

Several supraspinal mechanisms have been proposed for cross-education, including common improvements in head, eye, and trunk coordination during unilateral training [37], an updated motor plan that takes a bilateral course via crossed and uncrossed corticospinal fibres [38], an overflow of motor impulses from the trained to untrained hemisphere [3], and bilateral alterations in moto- and interneuron excitability caused by the afferent feedback of the exercising muscles [39]. To date, only a few studies have investigated the involvement of supraspinal circuits but it seems that the inhibitory neurotransmitter gamma-aminobutyric-acid (GABA) plays an important role in evoking cross-education [20,40-43]. GABAergic inhibitory interneurons constitute 10-25% of all cortical
neurons and play a major role in modulating the activity of pyramidal neurons [44]. Unilateral resistance training reduces the activity of GABA\textsubscript{A}-mediated inhibitory interneurons in the untrained M1 [40,41] and reduces GABA\textsubscript{B} receptor activity in the untrained M1 [20,41], ultimately resulting in an increased corticospinal output from the untrained M1 to the transfer muscles [40,42,45]. GABAergic interneurons not only mediate M1 excitability but regulate the neural activity in all areas of the cerebral cortex [44]. Therefore, it is likely that changes in GABAergic neurotransmission in areas other than M1 also contribute to cross-education.

The untrained sensorimotor cortex and trained temporal lobe are areas outside M1 that are involved in the cross-education of muscle force, as demonstrated in the only imaging study [46]. Changes in the trained and untrained hemisphere also suggest that interhemispheric interactions are important for cross-education. Indeed, a reduced interhemispheric inhibition from the trained to untrained M1 is associated with greater strength transfer [42] but does not preclude the involvement of interhemispheric connections other than M1. These connections might be between homologous pre-supplementary motor areas, supplementary motor areas, dorsal premotor cortices, and primary sensory cortices because these sensorimotor connections are also involved in motor control [47]. However, these structures and interhemispheric connections have never been examined in the context of the cross-education of muscle force.

1.4 How to facilitate the amount of cross-education

The training program should provide an adequate training stimulus that induces a high amount of cross-education. What matters for the cross-education magnitude are contraction type [14] as well as contraction speed and the number of contractions [48]. There are no studies that compare the amount of cross-education between static and dynamic resistance exercises but the increased afferent input concerning the velocity, position, and visual perception of a moving limb might enhance the force transfer [49]. Focusing on dynamic movements, lengthening vs. shortening muscle contractions produce three times more cross-education in the lower extremity [14] and 47 vs. 28% cross-education in the upper extremity [43]. The higher amount of cross-education for lengthening contractions was accompanied by increased corticospinal excitability of the untrained M1 and reduced GABA\textsubscript{A} and GABA\textsubscript{B}-mediated intracortical inhibition [43], again indicating that GABAergic receptors are involved in the cross-education of muscle force. Training at a higher contraction speed (140 vs. 50 °/s) and with more contractions (~21 vs. ~7 contractions per training)
also facilitated cross-education [48]. Thus, most favourable for inducing cross-education would be a unilateral resistance training program with a high number of lengthening muscle contractions performed at a high contraction speed.

The magnitude of cross-education is modest [10,11] and therefore there is a need to augment the force transfer. On the premise that sensory input is essential for the acquisition of new motor skills [50], it is hypothesized that augmented sensory feedback using a mirror can amplify the cross-education of muscle force [28], but evidence is yet lacking.

In mirror training the mirror reflection of the training hand is superimposed over the untrained hand, so that viewing the exercising hand in the mirror creates the illusion that the untrained stationary hand is moving. Mirror training can augment the cross-education of motor skills [51,52] by activating elements of the perceptuomotor system that are not activated when unilateral training is performed without a mirror [53]. This unique brain activation enhances the input to the M1 and could therefore amplify cross-education. Indeed, an increase in corticospinal excitability of the ipsilateral M1 was observed acutely [54] and after a single bout of mirror training [55] and resulted in the augmented transfer of a ball rotation task compared to training without a mirror [55]. The unique elements that are activated by mirror-viewing are involved in the allocation of attention, motor planning, and action execution, with a mediating role for the mirror-neurons system [53]. More specifically, mirror neurons discharge action potentials with both action observation and action execution [56], and it is possible that action observation results in altered corticospinal excitability reflecting the pattern of muscle activity of the observed action [57]. Altogether, there is evidence that mirror training can augment the transfer of motor skills but it is yet unknown what the underlying mechanisms are and whether mirror training is beneficial for augmenting the inter-limb strength transfer.

1.5 Clinical applications of cross-education

Unilateral orthopaedic injuries and neurological disorders result directly (e.g., after a stroke) or indirectly (e.g., after immobilization following a fracture) in strength loss, atrophy, and decreased muscle activation [58-61]. Cross-education can be a meaningful tool in restoring symmetry between the weakened and intact limb by making use of the evolutionarily conserved bilateral circuits that are also involved in inter-limb coordination [62,63]. The idea is that cross-education added to the
standard care program can help to accelerate the recovery of the impaired side by resistance training the non-impaired side.

First evidence for the clinical relevance of cross-education comes from immobilization studies in subjects without a fracture [64-67]. Immobilization resulted in decreased voluntary muscle force and muscle thickness, but these decreases could be prevented when resistance training the free limb [64,65,67]. In addition, the maintenance of muscle force in the immobilized limb was mediated by changes in M1 activation [66] and corticospinal excitability [67], suggesting that the clinical benefits of cross-education materialize at different levels in the nervous system.

Inter-limb force transfer can accelerate rehabilitation of unilateral orthopaedic injuries [19,68]. Cross-education added to standard care increased wrist strength and range of motion 12 weeks post wrist fracture [19] and reduced the quadriceps strength deficit between the anterior cruciate ligament (ACL) reconstructed leg and the non-injured leg nine weeks post-surgery [68]. Although these results are promising, self-reported pain and function, the most important clinical outcome, did not differ between the standard care group and the standard care plus cross-education group [19]. Although patients might not perceive their function or pain to be better, a stronger and more mobile joint will be related to prevention of re-injury, but there is no data on this yet.

Patients who suffer a stroke may also benefit from the cross-education of voluntary muscle force [69,70]. Cross-education may be most beneficial for patients with a severe paresis whose musculature on the paretic side is too weak to engage in resistance training. Indeed, four stroke patients were unable to produce meaningful dorsiflexion torque prior to the intervention but were able to do so after resistance training the non-paretic side [69]. Similar results have been observed for the upper extremity where unilateral resistance training of the non-paretic wrist resulted in increased range of motion of the paretic wrist [70]. Neural adaptations, especially in the corticospinal path, seem to accompany the paretic wrist’s improvement [70]; however, more convincing evidence is needed since corticospinal adaptations were only measured in two stroke patients.

1.6 Thesis objectives and outline

The first aim of this thesis is to examine the role of cortical and corticospinal circuits in the cross-education of voluntary muscle force and to determine if mirror training can augment this cross-education by modifying these
circuits. The second aim is to exploit further the benefits of cross-education in patients who suffered a unilateral orthopaedic injury. Chapter 2 examines the role of the mirror-neurons system in cross-education and introduces the idea that mirror training has the ability to augment the cross-education of voluntary muscle force. In addition, chapter 2 identifies gaps in knowledge of which several will be addressed in the remainder of this thesis. Chapter 3 examines the role of cortical and corticospinal circuits at rest as well as during unilateral forceful contractions under no-mirror and mirror conditions. Chapter 4 tests the hypothesis that mirror training can augment the cross-education of voluntary muscle force by additionally modulating cortical and corticospinal excitability compared to unilateral resistance training without a mirror. To bridge the research conducted in healthy adults and patients with a unilateral impairment, Chapter 5 describes the differences in neuromuscular function between the injured and non-injured leg of ACL patients awaiting surgery as well as healthy control legs. Chapter 6 examines the functional and neuromuscular benefits of cross-education in patients who exhibit unilateral leg muscle weakness following ACL reconstruction. Chapter 7 is a general discussion of the reported findings in this thesis, including clinical implications and directions for future research.

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