Inter-limb mechanisms and clinical relevance of cross-education in humans
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Chapter 7

General discussion
7.1 Main findings

Historical data for over 100 years suggest that unilateral resistance training can produce a cross-education effect corresponding to 52% of the force gained on the trained side [1]. Since the first studies on cross-education several mechanism have been postulated, like increased will-power and improvements in eye, head and trunk coordination [2]. The recently proposed mechanisms are that motor engrams of the practiced movement either are located in both hemispheres or are accessible for both hemispheres [3]. Our review and the resulting model expanded this current view in as much that the mirror-neuron system, connecting sensory neurons activated by viewing a movement and motoneurons executing this movement, also contributes to cross-education [chapter 2]. As hypothesized in chapter 2, mirror-viewing acutely reduced the effect of GABAergic inhibitory interneurons [chapter 3] and chronically amplified cross-education of muscle force and affected GABAergic inhibitory circuits [chapter 4]. A clinical examination of these neurophysiological findings showed that anterior cruciate ligament (ACL) patients awaiting surgery exhibited bilateral neuromuscular impairments in dynamic balance and voluntary quadriceps activation compared to controls [chapter 5]. Exploration of the cross-education benefits in patients who suffered quadriceps weakness in the reconstructed leg after ACL surgery revealed that additional resistance training of the non-injured leg’s quadriceps did not accelerate the rehabilitation process [chapter 6].

7.2 Neural substrates involved in cross-education

A review of the literature revealed that changes in cortical activation, motor cortical excitability, and corticospinal excitability all contribute to the cross-education of muscle force [chapter 2]. There are a limited number of chronic studies that examined the neural mechanisms of cross-education and therefore we extended our search to acute studies. The neural structures that were modulated during an acute bout of forceful unilateral muscle contractions also showed adaptations following multiple training sessions [chapter 2]. A good example is the acute as well as chronic increase in excitability and activity of the primary motor cortex (M1) in both hemispheres. The conceptual model of 21 reviewed studies in chapter 2 revealed that structures in the frontal and temporal lobe as well as the cerebellum are involved in cross-education. The cerebellum serves as a reference control system that adjusts motor performance by comparing the executed with the intended movement [4,5]. Continuous updates of the internal model improve motor coordination by a more accurate timing of agonist, antagonist, synergist, or postural muscle activation. Retrieval of this internal model via interhemispheric and
fronto-cerebellar interactions could facilitate intermanual transfer [6-8]. Frontal structures like the premotor areas, supplementary motor area (SMA), and M1 determine and refine the somatosensory goal of the action and establish the best motor program for achieving that action [9,10]. The inferior and middle temporal gyri compare the predicted with the observed visual consequences of a motor command and provide a higher-order visual description of the observed action [11,12]. The superior parietal lobe, a key structure of the mirror-neuron system that codes the goal of the action and the specific motor program for achieving that action [11,12], is not involved in the cross-education of voluntary muscle force, which suggests that other circuits than the mirror-neurons system are also important for inducing cross-education [chapter 2]. Interhemispheric effects, as indicated by the bilateral contribution of premotor areas, SMA, and M1 to cross-education, are likely to affect these circuits [3].

Many acute and chronic studies incorporated in our conceptual cross-education model specifically focused on the M1. It is well known that unilateral forceful muscle contractions increase the corticospinal excitability of the M1 ipsilateral to the movement, as illustrated in chapter 3. For the first time we showed that corticospinal excitability to the homologous agonist and antagonist muscle was increased during forceful dynamic wrist flexion movements with the right hand compared to rest [chapter 3]. An increase in corticospinal excitability during forceful unilateral muscle contractions is associated with a reduction in short-interval intracortical inhibition (SICI) in the ipsilateral M1, a GABA\textsubscript{A}\textsuperscript{-} mediated intracortical inhibitory circuit [13,14]. These acute modulations in ipsilateral M1 corticospinal excitability and SICI become chronic after multiple weeks of unilateral resistance training, as illustrated in chapter 4 and other studies [15,16]. Lengthening muscle contractions even modulate corticospinal excitability and SICI to a greater extent than shortening muscle contractions [14,15]. The contribution of these circuits to the cross-education of voluntary muscle force seem evident but correlation analyses between changes in ipsilateral M1 excitability and the amount of cross-education are lacking, except in one study where the increase in corticospinal excitability of the ipsilateral M1 was positively correlated with the amount of cross-education and this correlation became stronger with an increasing number of practice sessions [17]. In the same study they found a correlation between the reduction in interhemispheric inhibition (IHI) from the trained to untrained M1, a measure of interhemispheric glutaminergic connectivity, and the magnitude of cross-education [17]. We found that the cross-education of muscle force was accompanied by an increase in IHI but the sample size was too small to calculate correlations [chapter 4]. It is hard to interpret these contrasting findings but certainly
there is evidence for the involvement of interhemispheric connections in cross-education. Connectivity analyses between intrahemispheric and interhemispheric sensorimotor areas will shed further light on the neural mechanisms involved in cross-education.

### 7.3 Neural substrates involved in mirror training

Chapter 2 and another recently published literature review [18] show that three functional networks contribute to the mirror-induced changes in motor skill learning. First, attentional resources like the dorsolateral prefrontal cortex, superior posterior parietal cortex, and the primary and secondary somatosensory area are modified to resolve the perceptual incongruence between proprioceptive and visual feedback evoked by the mirror illusion of a moving hand [19-21]. Second, the superior temporal gyrus and premotor cortex, which show a mirror-induced increase in neural activity, are part of the mirror-neurons system and connect the neurons involved in visual perception and action execution [22,23]. The motor network is the third functional network that is modulated by mirror-viewing. Observation of low-force hand and finger movements in a mirror increased ipsilateral corticospinal excitability [24] and M1 activity [25] corresponding to the resting hand behind the mirror. However, a four-day mirror training intervention did not result in chronic excitability changes of the ipsilateral M1 nor did it modify the amount of IHI from the contralateral to ipsilateral M1 [26]. The anterior part of the corpus callosum is involved in interhemispheric inhibition and contributes to the integration of perception and action [27]. It is therefore surprising that mirror training did not affect interhemispheric inhibition.

Chapters 3 and 4 provide further insights into the role of the ipsilateral and contralateral M1 in mirror training for forceful dynamic unilateral muscle contractions. The ipsilateral M1 showed an acute and muscle specific reduction in SICI [chapter 3] and a chronic reduction in contralateral silent period duration, a GABA_B-mediated intracortical inhibitory circuit [chapter 4]. IHI from the trained to untrained M1 was increased following three weeks of mirror training and suggests a shift in attention from the M1 involved in unilateral resistance training to the M1 associated with the mirror image [chapter 4]. No mirror-induced changes were observed for corticospinal excitability, which indicates that mirror training only affects the excitability of GABAergic inhibitory interneurons.

An integration of the three functional networks (i.e., attentional resources, the mirror-neuron system, and the motor network) is needed to create a unified model of how mirror training might work. The conceptual model
developed in chapter 2 is a first step to understand how motor practice while viewing the mirror image of an active limb can magnify cross-education. Functional connectivity analysis can help to detect common activation patterns in brain regions that are connected via transcallosal and/or intrahemispheric pathways [28]. One mirror training study has already used this analysis and found an increased coupling between the premotor cortices and the left supplementary motor area following four days of motor practice with the right hand [23]. A recent in vivo portrayal of transcallosal white matter projections between homologous and non-homologous areas of the cortical motor network can be used for developing hypotheses and computational models that further disentangle the neural mechanisms of mirror training [29,30].

7.4 Behavioural outcomes of mirror training: optimistic view

Motor tasks that are performed in mirror training are gross, functional, and fine motor movements that require low voluntary muscle forces [chapter 2]. It is interesting to note that stroke patients do not only suffer from impaired motor function but also from muscle weakness on the more- and less-affected side [31], suggesting that there is a need to also focus on forceful muscle contractions in stroke rehabilitation. Resistance training of the more-affected side can improve muscle force and motor function without increasing spasticity and pain [32-35]. However, one of the difficulties with stroke is that the muscles on the more-affected side are often too weak to engage in a resistance-training program [36]. To overcome this problem, stroke patients can perform unilateral resistance exercises with the less-affected side to increase muscle force on the more-affected side, i.e., cross-education [37,38]. The application of the cross-education of muscle force is not only relevant for stroke but also for patients recovering from a fracture [39], anterior cruciate ligament (ACL) reconstruction [40,41], arthroplasty, fibromyalgia, and arthritis. To increase the potential of cross-education, we hypothesized that a combination of mirror training and unilateral resistance training could amplify the magnitude of cross-education [chapter 2]. As expected, forceful dynamic wrist flexion movements with a mirror increased cross-education by 27% compared to training without a mirror [chapter 4]. The increase in the trained wrist’s muscle force was 72% and similar across groups [chapter 4]. These results indicate that mirror training while using unilateral forceful contractions can be a successful tool in restoring bilateral weakness after unilateral orthopaedic and neurological disorders.
7.5 Behavioural outcomes of mirror training: pessimistic view

The efficacy of mirror training was first examined in nine upper extremity amputees who experienced phantom limb pain [42]. Mirror-viewing of the exercising intact limb created the vivid kinaesthetic sensation of a moving phantom limb which reduced phantom limb pain [42,43]. Clinicians realized that this simple, non-pharmaceutical, and inexpensive form of therapy could not only help amputees but also patients with other unilateral disorders like hemiparesis following a stroke [44-46], complex regional pain syndrome [47,48], deterioration of hand function after nerve reconstruction [49], and mobility impairments following a wrist fracture [50]. However, recent systematic reviews revealed that mirror training, as adjuvant to standard therapy, has no additive effect on treating phantom limb pain [51] and the complex regional pain syndrome [52] but improves motor function and activities of daily living in stroke patients [53,54]. However, it could also be that unilateral training itself improves motor function after a stroke and that the additive value of a mirror is limited [55].

The cross-education data from mirror training studies in healthy subjects are not convincing either. Two of six studies showed that mirror training did not facilitate the transfer of motor skills compared to unilateral training without a mirror [56,57]. Three studies revealed a mirror-induced cross-education effect but results could not be replicated [58] or the behavioural data were expressed relative to baseline [23,26], which leaves open the possibility that performance improvements were driven by baseline differences. The sixth study [chapter 4] comprised forceful monotonic wrist flexion contractions and differs considerably from the five studies that used low-force but highly variable movements, not in the last place because motor skill training and resistance training are associated with different neural adaptations [59]. Nonetheless, chapter 4 demonstrated that mirror training amplifies the cross-education of maximal wrist flexion force by 1.7 Nm (13%) but this mirror-induced effect was only training specific and did not reach the clinically meaningful difference of 20% for grip strength [60]. Obviously, grip strength is not similar to wrist flexor strength but the 20% threshold gives at least an indication in the absence of reference data for wrist flexor strength. Altogether, evidence for the additional value of mirror training over unilateral training without a mirror is weak and the mirror-induced effect is probably too small compared to the dysfunction caused by the clinical conditions that the mirror-augmenting effect may just never reach a functionally meaningful level.
7.6 Unilateral ACL injury has bilateral effects

To apply the cross-education principle to a clinical condition, it is necessary to characterize the functional state of each limb at the start of the intervention. Chapter 5 quantifies the magnitude and nature of any neuromuscular deficit in the non-injured leg following a unilateral ACL injury. The non-injured leg revealed impairments in dynamic balance and voluntary quadriceps activation but the other neuromuscular functions, i.e., maximal quadriceps and hamstring torque, quadriceps force control, knee joint proprioception, static balance, and single-leg hop distance, were not affected. ACL rehabilitation programs should continue to focus on the injured leg and the non-injured leg can serve as adequate reference to monitor the neuromuscular recovery of the injured leg.

Return to sport is the main goal of ACL rehabilitation and often requires ACL reconstruction to restore knee stability in the sagittal plane. Traditional ACL rehabilitation programs, like in chapter 6, are designed to improve neuromuscular function and side-to-side symmetry [61]. Chapter 6 illustrates how neuromuscular functioning of the reconstructed and non-injured leg develop in the initial six months after surgery. Neuromuscular impairments were observed 5 and 12 weeks post-surgery, for example in maximal quadriceps and hamstring torque and dynamic balance, but not six months post-surgery [chapter 6]. Quadriceps force control, dynamic balance, and maximal quadriceps and hamstring torque were even improved six month post-surgery compared to pre-surgery [chapter 6]. These data illustrate that neuromuscular functions in the reconstructed and non-injured leg can recover within six months post-surgery. However, only 65% of the rehabilitated ACL patients return to their pre-injury sport level [62] and 15% sustains a second ACL injury on the ipsilateral (7%) or contralateral (8%) side [63]. In addition to neuromuscular functions, ACL rehabilitation should target biomechanical and neurophysiological alterations to improve function and reduce the incidence of re-ruptures [64,65].

7.7 Cross-education to accelerate the rehabilitation after ACL reconstruction

Chapter 6 examines whether cross-education, as an adjuvant to standard care, can accelerate the return to full capacity after an ACL surgery. Rehabilitating quadriceps force by cross-education could be relevant for ACL patients because these patients present bilateral quadriceps weakness after an ACL surgery [66-69] and the weakness is associated with worse self-reported function [70-72] and physical performance
up to 40 months after surgery. Against predictions laid out in chapters 1, 2, 3 and 4, chapter 6 shows that cross-education training did not accelerate the recovery after ACL reconstruction nor did it slow down the recovery process.

Convincing evidence from high-quality research is needed because four of five orthopaedic studies were poorly controlled and published misleading results in favour of the cross-education group. To exemplify, the type of upper extremity injuries differed between the cross-education and control group and the limb’s pre-surgery status was not reported [76,77], data of the non-injured leg receiving the cross-education training were lacking [41,76,77] or incorrect (i.e., recalculation revealed that quadriceps force improved 5-6% for the cross-education groups and 17% for the control group) [40], and all four studies experienced baseline differences between groups [40,41,76,77]. Only one study was well-controlled and showed a small clinical effect of cross-education following a wrist fracture for handgrip strength but not for self-reported pain and function [39]. The clinically important difference for handgrip strength was 20% [60] and was reached at 12 weeks post-fracture (34% higher for the cross-education than standard care group) but not at 26 weeks post-fracture (17%) [39]. The cross-education effect in healthy but immobilized subjects was 11-48% [78-81] and seems to be smaller in orthopaedic patients, which suggests that injury-related factors like pain and swelling affect the working mechanism of cross-education.

The smaller magnitude and hence smaller clinical effect of cross-education might be caused by injury-induced neurophysiological changes. The cross-education of muscle force is mediated by neural substrates that sub-serve the M1 to increase the neural output to the homologous non-exercised muscles [chapter 2 and 4]. However, an injury affects the structure and function of the brain [82-84], which perhaps reduces the adaptability of the brain to induce cross-education. To illustrate, the loss of sensory receptors in the ACL lesioned knee affect the afferent feedback [85] and result in a reorganization of cortical sensorimotor areas [86-89]. These cortical changes are observed in the hemisphere corresponding to the ACL deficient [86] or reconstructed leg [88,89] but also bilaterally [87]. In addition, the M1 area is reduced by about 50% after at least four weeks of immobilization following a fracture around the ankle joint [90]. Altogether, an ‘injured’ brain might become less sensitive to sensory cues and motor stimuli and would decrease the responsiveness to a motor intervention like cross-education. Animal models of stroke certainly underscore such an analysis, considering the unfavourable effects of unilateral motor practice [91,92].
7.8 Limitations and further recommendations

This thesis has several limitations. First, transcranial magnetic stimulation was used in chapters 3 and 4 to examine the role of different M1 paths in cross-education with and without a mirror, without measuring the involvement of other brain areas. Connectivity analyses using fMRI and EEG would complement TMS studies for investigating the role of somatosensory areas and elements of the mirror-neuron system in the cross-education of voluntary muscle force. Second, the clinical applications of cross-education are of interest but it is also necessary to understand how an injury affects the neural structures cross-education would subsequently target. Pain, swelling, receptor loss, and immobilization following orthopaedic injuries affect the brain and might change the brain’s adaptability to unilateral resistance training. Third, chapters 5 and 6 show that the neuromuscular function after an ACL lesion and reconstruction is surprisingly good but it might be that ACL patients have different movement patterns than non-injured controls and are therefore more susceptible to sustain an ACL injury [93]. Non-contact ACL injuries are often the result of excessive quadriceps loads and/or knee moments in the frontal and transversal plane during acceleration and declaration motions [94]. Future research should focus on biomechanical analyses and interventions that detect and target movement abnormalities which, when untreated, would have increased the risk to rupture the ACL.

7.9 Conclusions

Augmented sensory inputs by viewing the dynamically and forcefully contracting right hand in a mirror reduces the excitability of inhibitory interneurons in the right M1 corresponding to the homologous agonist but not in the antagonist muscle of the resting left hand. Fifteen of these training sessions (48 contractions each) resulted in 27% more cross-education than training without a mirror and affected GABAergic inhibitory paths in the M1 targeting the muscle that showed cross-education. The literature review increases the understanding of the cortical and corticospinal circuits that mediate cross-education with a role for the mirror-neuron system in mirror training but not in unilateral training without a mirror. Knowledge about inter-limb mechanisms and function is extensive for healthy subjects but scarce for ACL patients. We showed that the neuromuscular function of the ACL patients’ injured leg is impaired but that the function of the non-injured leg is comparable to healthy controls, except for voluntary quadriceps activation and dynamic balance. Six months of standard care after ACL reconstruction restored self-reported function and neuromuscular function relative to pre-surgery but cross-education training, as adjuvant to standard care, did not
further improve recovery. Although this thesis helps to disentangle the underlying neural mechanisms and clinical relevance of cross-education, there still is a substantial gap in knowledge about how the homologous contralateral muscles after unilateral training exploit the extra brain activation to allow healthy subjects and patients to generate more force.

References


