SUN, Liang, WANG, Yi, LUO, Lanfang, YANG, Yi and LUO, Jiong. Cross-education Mechanisms and Clinical Rehabilitation Research: A Literature Review. Quality in Sport. 2024;35:56330. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.35.56330
https://apcz.umk.pl/QS/article/view/56330

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

Received: 21.10.2024. Revised: 12.11.2024. Accepted: 29.11.2024. Published: 29.11.2024.

Cross-education Mechanisms and Clinical Rehabilitation Research: A Literature Review

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Abstract: In recent years, cross-education has garnered significant attention in the fields of clinical rehabilitation and sports training. Since the discovery of CE, a growing number of studies have focused on understanding its characteristics for deeper insight and application. Two theoretical models currently attempt to explain this adaptive mechanism and are mutually compatible: the "cross-activation" model, which suggests that adaptations to unilateral exercise extend to the contralateral side of the body, and the "bilateral-access" model, which posits that the motor patterns of unilateral activities are replicated on the opposite side.When formulating clinical rehabilitation prescriptions, factors such as the patient's gender and training experience must be considered. Males and inexperienced patients seem to benefit more significantly. High-intensity eccentric unilateral resistance training is recommended for rehabilitation exercises, ideally over a period exceeding four weeks with intervals of 1-2 days between sessions. Each intervention should include 2-3 minutes of rest between sets to allow sufficient recovery time, thereby preventing neuromuscular fatigue and enhancing the benefits of CE, ultimately promoting and accelerating the rehabilitation process.

Keywords: Cross-education; unilateral training; neural mechanism; clinical rehabilitation

1. Introduction

Cross-education refers to the phenomenon where strength gains in an untrained limb are observed following unilateral resistance training on the opposite limb[1]. As early as 1894, Scripture and his colleagues demonstrated using a simple dynamometer that unilateral strength training can enhance performance in the same movement of the untrained contralateral limb. Since the term CE was coined, it has been replicated in numerous studies, encompassing both strength and motor skill transfer[2-4]. This phenomenon is also known as cross-training, cross-effect, CE, contralateral learning, or interlimb transfer[5, 6]. CE can be a useful method to increase strength in both the contralateral and ipsilateral limbs, as well as in homologous and heterologous muscles, especially when unilateral limb movement is restricted[7-10]. Despite long-standing interest in this phenomenon, there is little consensus on the underlying neural mechanisms.

Why is it important to fill this knowledge gap? For example, falls resulting in fractures pose significant risks for elderly individuals, as the loss of specific muscle strength or general ability due to limb immobilization can hinder daily tasks and independent living. Even in young individuals with ample functional reserves, three weeks of immobilization can lead to a strength decrease of about 50% of the initial strength[11]. However, training the uninjured limb during immobilization can mitigate this loss of function[12-14].

The specific benefits of CE are crucial for clinicians seeking to use it as a rehabilitation method. Given its therapeutic potential, it is essential to establish a principled basis for the mediating mechanisms, upon which to design interventions. This includes determining which unilateral resistance training prescriptions (duration, frequency, load intensity, and contraction type) optimize strength gains in the untrained limb and verifying whether factors such as gender, body region, and health level influence CE benefits. This evidence is necessary for developing clinical CE prescriptions and adjusting these measures to meet individual needs.

2. Phenomenon characteristics

In recent years, CE has garnered significant attention in the fields of clinical rehabilitation and sports training. Since the discovery of CE, a growing number of studies have focused on understanding its characteristics for deeper insight and application.

2.1 Power amplification

The magnitude of CE is proportional to the increase in muscle strength of the trained limb, with the contralateral strength gains being approximately 60% of those in the trained limb[15, 16]. Green's study not only observed the presence of CE after six weeks of unilateral training but also found that the strength gains in the contralateral limb were enduring and related to neuromuscular adaptation, indicating motor learning in the contralateral limb. While the study identified a relationship between the magnitude of CE and the strength gains in the trained limb, it did not elaborate on whether training the non-dominant limb affects the strength gains in the dominant limb, thus lacking a precise description and discussion of the directionality of CE. Zhou's analysis of nearly 40 studies on strength changes in the trained and contralateral limbs revealed that strength gains in the contralateral limb are associated with those in the trained limb[16]. The extent of CE is proportional to the increase in strength of the trained limb, averaging about 60% of the strength gains in the trained limb.

Therefore, in the application of CE, observing the strength gains in the trained limb can provide a convenient and quick assessment of the strength increase in the contralateral limb. This facilitates the evaluation of treatment effects and helps in scientifically formulating training loads for the dominant limb, enhancing the overall rehabilitation plan to improve the strength of the contralateral muscles and achieve the desired rehabilitation outcomes.

2.2 Training methods

Unilateral strength training using eccentric contractions significantly increases the strength of contralateral homologous muscles more than concentric contractions. Data show that after 12 weeks of training, eccentric training enhances contralateral quadriceps strength to three times the level achieved by concentric training. Moreover, the time to achieve CE effects is significantly shorter with eccentric training; six weeks of eccentric training can enhance contralateral homologous muscle strength by 40%, whereas concentric training requires 12 weeks to achieve similar results[17]. Compared to voluntary eccentric contractions, unilateral training with muscle electrical stimulation significantly increases muscle strength in both trained and untrained limbs. After the same training period, electrical stimulation training enhances the strength of trained and untrained limbs by 177% and 104%, respectively, while voluntary contraction training increases the strength of the same and opposite limbs by 54% and 23%[18]. Although unilateral electroacupuncture and manual acupuncture at specific points can both improve the strength of contralateral homologous muscles, the magnitude of strength improvement differs between the two methods[19]. After six weeks of unilateral acupuncture at Zusanli and Shangjuxu, electroacupuncture can increase contralateral ankle dorsiflexor strength by 32%, while manual acupuncture can improve it by 49%, with manual acupuncture showing a greater enhancement of contralateral muscle strength than electroacupuncture[20].

It has been found that strength training CE effects induced by motor imagery can occur in the abductor digiti minimi muscles. For instance, four weeks of unilateral motor imagery training can increase the strength of the same and opposite abductors by 22% and 10%, respectively[21]. Similarly, elbow flexor and ankle dorsiflexor muscles can also increase in strength through motor imagery training, although whether CE effects occur remains to be determined[22, 23].

2.3 Detection mode

The effectiveness of CE is not only related to the training itself but also to the consistency between the training and testing methods[24]. Zult et al. found that the effect of CE from a specific muscle contraction is specific, as using a different muscle contraction method during testing results in a much smaller CE effect[25]. Therefore, to maximize the benefits of CE, rehabilitation plans must consider the consistency between the training and testing methods. When clinical applications of CE do not yield ideal results, the alignment of training and testing methods should be evaluated to avoid missing the optimal treatment plan, thereby impacting overall treatment effectiveness.

Numerous studies have shown that strength gains are more significant when the muscle actions used in strength tests (eccentric, concentric, or isometric contractions) correspond to those performed during training[26-28]. In other words, the most pronounced CE effects occur when the muscle strength testing method aligns with the muscle training method. For example, after eccentric contraction training, the best results are achieved with eccentric strength testing. Therefore, when testing training results, selecting the corresponding testing methods based on different training methods can better apply the effects of CE in clinical evaluation and treatment.

3. Clinical application

With the implementation of national fitness programs and the increasing issue of an aging population in China, the number of patients with unilateral limb injuries and activity impairments is rising. Unilateral limb activity impairments are present not only in neurological conditions, such as post-stroke hemiplegia, but also in orthopedic conditions like unilateral knee osteoarthritis and ligament injuries. Even after surgery, the affected limb may still experience immobilization and limited activity during the early postoperative period. Early rehabilitation is crucial for improving patients' functional recovery and quality of life. Thus, ensuring muscle strength and activity function in the affected limb without violating immobilization principles is essential. CE can improve muscle strength and function in the non-dominant limb by training only the dominant limb. Numerous studies have shown that applying CE concepts in resistance training for post-stroke hemiplegic patients can enhance upper limb muscle strength and function, as well as improve lower limb function, thereby increasing rehabilitation efficiency and quality of life[29-31]. Additionally, CE has been applied in orthopedic rehabilitation for unilateral limb injuries, such as unilateral osteoarthritis and knee ligament injuries[32, 33], with results indicating that CE can promote early rehabilitation and significantly improve functional impairments.

3.1 Orthopedic rehabilitation

Most orthopedic conditions involve unilateral limb injury or immobilization. Prolonged inactivity can lead to muscle loss, atrophy, and even affect the overall function of the limb. Early rehabilitation is crucial for functional recovery and improving patients' quality of life. However, a major challenge in early rehabilitation is balancing "early immobilization" with "maintaining muscle strength and joint function." The concept of CE offers a new approach to address this issue, making early rehabilitation during immobilization feasible.

Currently, CE has been widely applied in the rehabilitation of unilateral limb injuries, osteoarthritis, ligament injuries, and other orthopedic conditions, showing significant effects. Research indicates that in healthy adults, after artificially immobilizing one limb, training the non-immobilized limb for three weeks can maintain the strength of the immobilized limb, preventing a significant decrease. Without training the non-immobilized limb, the strength of the immobilized limb decreases by 14.7% after three weeks[12]. Clinical studies by Shi Dongliang et al.[34] have shown that CE principles and techniques can be used in the rehabilitation of patients with Colles' fractures during immobilization. Training the grip strength of the unaffected hand and the range of motion of the wrist significantly improves the function of the affected hand after the cast is removed.Moreover, numerous studies indicate that when one limb’s joints or muscles are injured, the injury and dysfunction can affect both limbs, leading to decreased function in the unaffected limb[35, 36]. This suggests that training the uninjured limb may be an important measure to prevent further complications.

3.2 Neurological Rehabilitation

Neurological diseases often involve unilateral limb impairment or asymmetric muscle function, such as in hemiplegia and multiple sclerosis. These conditions significantly affect patients' quality of life. Enhancing the function of the non-dominant limb by leveraging the existing function of the dominant limb can greatly improve rehabilitation outcomes. The concept of CE offers a novel approach to address these challenges, and its role in the rehabilitation of neurological diseases is increasingly emphasized in clinical settings.

Although the mechanisms are not well understood, there have been many applications of healthy-side acupuncture in treating post-stroke hemiplegia[37]. Huang Liping and colleagues[38, 39] found in animal studies that very early electroacupuncture on the healthy side, compared to the affected side, can more rapidly promote the recovery of neurological function in rats with middle cerebral artery occlusion, reduce the infarct volume in the affected brain, and significantly increase the expression of insulin-like growth factor-1 (IGF-1) mRNA and protein levels in the ischemic cortex. Further studies by Yu Junhai and colleagues showed that early electroacupuncture on both the healthy and affected sides effectively upregulated the expression of brain-derived neurotrophic factor (BDNF) mRNA in bilateral cortices, with the healthy-side treatment resulting in a greater increase in BDNF mRNA expression in the ischemic cortex[40]. These findings suggest that early electroacupuncture on the healthy side can better initiate the neural repair and regeneration process in the ischemic cortex.

In 2013, Dragert et al.[41] discovered that six weeks of isometric resistance training of the ankle dorsiflexors on the healthy side in stroke patients with hemiplegia increased the strength of the ankle dorsiflexors on the affected side by 31.37%, thereby improving the walking ability of hemiplegic patients. Stroke-induced brain damage disrupts the balance between the hemispheres, affecting symmetrical functions like walking. A 2014 review[42] concluded that CE could restore limb symmetry and be used in the rehabilitation of orthopedic injuries and post-stroke hemiplegia, providing further evidence for the clinical application of CE.

4. Possible mediating mechanism

4.1 Research on neuro mediated mechanisms

A review of 16 studies indicates that unilateral strength training can induce CE, potentially causing changes in multiple cortical regions. Unilateral strength training in acute studies activates similar brain regions that exhibit adaptations following chronic interventions. For instance, areas such as the ipsilateral primary motor cortex (M1)[43-46], premotor cortex[44], supplementary motor area (SMA)[44, 45], cerebellar lobules[45, 47], and primary somatosensory cortex[43] are active during right-hand unilateral strength training and also participate in the chronic CE effect observed in the untrained left hand[14, 48-52]. This common activation suggests that brain regions active during one or multiple resistance training sessions contribute to the chronic cortical effects observed after CE. In other words, brain regions activated by acute unilateral muscle contractions also adapt after repeated sessions. Table 1 provides an overview of the brain regions involved in acute and chronic exercise training using the dominant right hand.

However, studies on how intra- and interhemispheric activation during unilateral muscle contractions facilitate strength CE are inconsistent, showing differences between chronic and acute research. During right-hand muscle contractions, short-interval intracortical inhibition (SICI) in the non-engaged right M1 significantly decreases[53-55]. However, Hortobágyi et al. found no decrease in SICI in the non-engaged right M1 after repeated strength training of the right first dorsal interosseous muscle (FDI). This suggests that SICI in the non-engaged right M1 does not validate CE following long-term training; perhaps the circuits involved in SICI have poor adaptability under these conditions. The discrepancy in SICI observed in acute vs. chronic training may be related to exercise load intensity, i.e., 80% maximal voluntary contraction (MVC)[53] vs. 10%, 30%, and 70% MVC[55], and contraction type, i.e., isometric contraction[53] and concentric contraction[54], as SICI in the non-engaged right M1 weakens with increasing load intensity and further reduces in isometric contractions compared to concentric contractions. Interhemispheric inhibition (IHI) from engaged to non-engaged M1 decreases during acute and chronic right wrist isometric contractions, with IHI strength decreasing as unilateral strength training sessions increase. In contrast, Kidgell et al. found no changes in the ipsilateral silent period (iSP) within the biceps brachii (BB), suggesting no IHI changes after chronic unilateral resistance training. One possible explanation for this observed contrast is differences between the two cortical inhibition circuits, indicating that circuits mediating IHI are more actively involved in CE than those involved in iSP. Disrupting the right dorsal premotor cortex (dPMC) increased mirror movements during left hand isometric contractions[56, 57], suggesting that IHI values between left and right dPMC increase when the right dPMC is not disrupted. In these studies, the lack of mirror movements when the right dPMC was intact reinforced this view. Hoy et al.[58] reported that, besides the lack of mirror activity, the ipsilateral silent period during little finger abduction was significantly delayed compared to the contralateral silent period, indicating that mirror activity may be inhibited through IHI.Since decreased IHI facilitates mirror activity, and CE is observed only during dominant right-hand training, this suggests that CE benefits are much greater for right-handed individuals during dominant hand training[7].

Chronic strength training of the right arm results in significant increases in activation of the left inferior temporal gyrus, middle temporal gyrus, and medial occipital cortex[48, 49], but this activation pattern does not appear in acute studies. The expanded activation of the trained brain's frontoparietal region and reduced IHI after training highlight the importance of interhemispheric communication from the trained brain to the untrained brain. Communication between the trained and untrained hemispheres may lead to an improved motor plan, providing a reference for the untrained limb to prepare and execute future actions. Figure 1 presents a conceptual model of CE induced by unilateral muscle contractions of the right upper limb, based on a literature review and previously reported CE models[5, 7, 25]. This model identifies brain regions connecting the two hemispheres, playing a hypothetical (grey arrows) or validated (black arrows) role in CE from the trained right arm to the untrained left arm. The left hemisphere is shown on the left and the right hemisphere on the right. Shaded areas indicate brain regions involved in CE; darker shading indicates stronger evidence. Evidence for left hemisphere structures: medial frontal gyrus[47], caudal cingulate cortex[44, 45], supplementary motor area[44, 45], dorsal premotor cortex[44, 49], ventral premotor cortex[44, 49], primary motor cortex[14, 44-48, 51, 58-61], ventral somatosensory cortex[48], middle temporal gyrus[48], inferior temporal gyrus[48], lateral cerebellum[45, 48], posteromedial cerebellum[45, 48], medial occipital gyrus[48, 49]. Evidence for right hemisphere structures: caudal cingulate cortex[45], supplementary motor area[44, 45], lateral premotor cortex[44], primary motor cortex[14, 44-46, 48-52, 54, 55, 58-60], primary somatosensory cortex[48], superior temporal gyrus[47], anterior cerebellar lobules[45, 47], posteromedial cerebellum[45, 48], medial occipital gyrus[48].

There is insufficient evidence to support the involvement of the parietal lobe in CE, suggesting that other circuits are also important for eliciting CE, as mentioned earlier in this section. Carroll et al.'s model suggests that interhemispheric connections between different brain structures play a significant role in the CE of muscle strength. However, only two TMS studies have shown that during right-hand isometric contractions, IHI from the left to the unengaged right M1 decreases[53, 55]. From two additional TMS studies that did not directly test CE benefits, we can infer that interhemispheric connections between the left and right prefrontal cortices may also contribute to CE[56, 57]. fMRI and TMS studies have found that during right-hand isometric contractions, both M1, primary somatosensory cortex, premotor cortex, posterior cingulate cortex, and SMA are active in both hemispheres, suggesting that activation occurs simultaneously and is mediated by either interhemispheric spillover or both mechanisms. While interhemispheric plasticity is considered a possible mechanism for CE[5, 53], it remains unclear where and at what stage such transfer occurs. Imaging during unilateral strength training detected bilateral activation of M1 when the specific movement program for achieving the action goal was transmitted via corpus callosum connections from the left to the right frontal-parietal areas. Two fMRI studies observed bilateral M1 activity during right-hand isometric contraction training[44, 58], and six studies found that after repeated strength training, activation in the untrained right M1 increased[48, 49] or corticospinal excitability increased[14, 51-53]. Along with significant strength increases in the untrained left hand, these results support the cortical mechanisms mentioned, but more research is needed to verify the transcallosal connections in CE to establish a clear model.

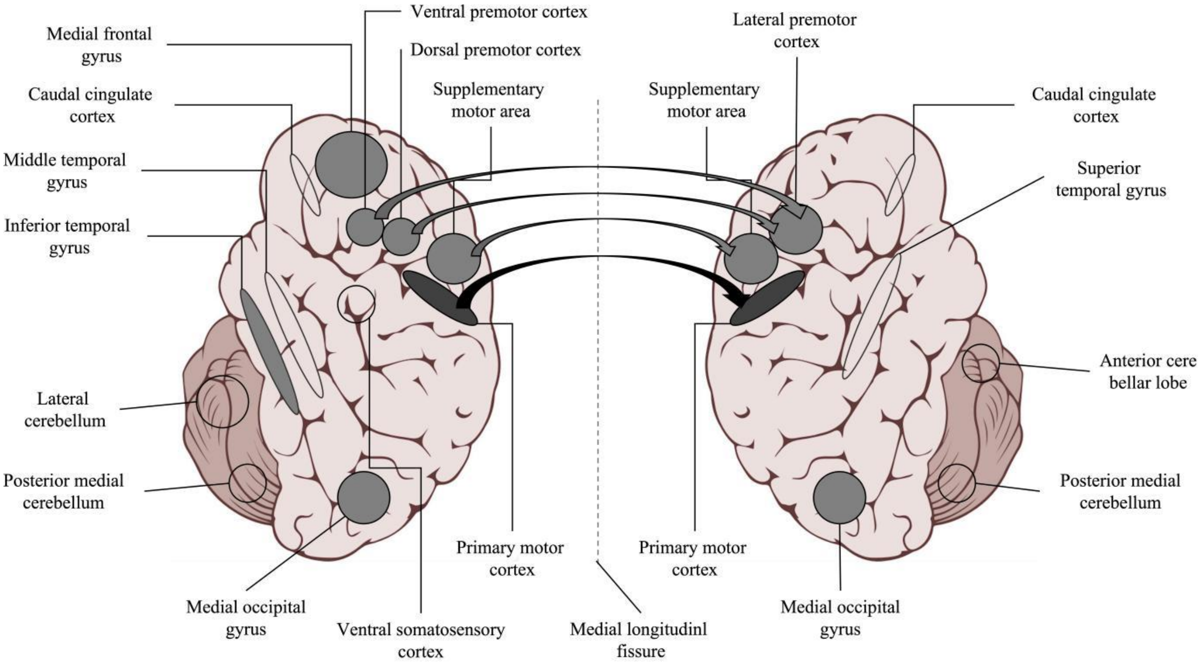

Figure 1. CE conceptual model

Table 1 Activate brain regions through Unilateral resistance training and habitual right arm strength training

Study	Type	Intervention methods	Activated area of the left hemisphere brain	Activated area of the right hemisphere brain
Bologna et al., 2012	Acute	Bounce the finger at maximum acceleration	M1	Not tested
Cramer et al., 1999	Acute	Perform right and left index finger tapping	Precentral gyrus	Precentral gyrus
Farthing et al., 2007	Chronic	Maximum equidistant contraction of the right ulnar side for 6 weeks, 4 times a week	Ventral M1 Ventral somatosensory cortex Anterior middle temporal gyrus Posterior middle temporal gyrus Inferior temporal gyrus Medial occipital gyrus Posterior medial cerebellum Lateral cerebellum	M1 Primary somatosensory cortex Medial occipital gyrus Posterior medial cerebellum

Farthing et al., 2011	Acute	Perform maximum equidistant grip contraction with the right hand	Premotor cortex Medial occipital gyrus	M1
Foltys et al., 2003	Acute	The left hand performs 60 consecutive grip strength contractions at a frequency of 0.8 Hz in both a stationary state and a clenched fist state	Medial frontal gyrus M1	Superior temporal gyrus Anterior cerebellar lobe
Hortoba´gyi et al., 2010	Chronic	50 episodes of autonomous contraction of the right first interosseous dorsal side were performed at 80% intensity, for a total of 20 training sessions	Not tested	M1
Hoy et al., 2007	Acute	Perform maximum voluntary contraction of the abductor muscles	M1	M1
Kidgell et al., 2011	Chronic	80% RM training for the right elbow flexor muscle, 3 times a week for a total of 4 weeks (12 sessions in total)	M1	M1
Lee et al., 2009	Chronic	Perform maximum autonomous isometric wrist extension and contraction on the right wrist for 4 weeks	Not tested	M1
Lee et al., 2010	Acute	Perform index finger abduction and bouncing with the right hand	M1	M1
Muellbacher et al., 2000	Acute	Contraction of abductor pollicis muscle	Not tested	M1
Newton et al., 2002	Acute	Isometric extension of wrist joint	SMA	SMA
Pearce et al., 2012	Chronic	Perform three weeks of isokinetic elbow flexion training	M1	M1
Perez and Cohen, 2008	Acute	Isometric contraction of wrist joint	Not tested	M1
Sehm et al., 2010	Acute	Isometric contraction of wrist joint	M1 SMA Caudal cingulate cortex Cerebellum (lobule IV)	M1 SMA Caudal cingulate cortex Cerebellum (lobule IV–V)
Zijdewind et al., 2006	Acute	Perform maximum voluntary contraction of the flexor muscles on the left and right elbows respectively	M1	M1

M1 primary motor cortex, SMA supplementary motor area

4.2 The Role of Primary Motor Cortex: "Cross-Activation" Mechanism

In the quest to elucidate the neural mechanisms mediating CE, the primary focus so far has been on brain regions most significantly involved in generating motor output. Many investigations seem to be based on the assumption that CE is mediated by changes in the state of intracortical circuits within the M1 of the trained limb. Emphasizing the role of M1 appears well-motivated, primarily because the expression of the CE effect would be impossible without corticospinal outputs, which mainly originate from the activation of cortical neurons and somas in the caudal region of M1[62]. Therefore, it is necessary to consider the potential intermediary role of adaptations that regulate the state of circuits within M1 or influence the excitability of subsequent corticospinal projections. The most apparent anatomical structure likely to induce these changes is the corpus callosum (CC)—the largest white matter bundle in the human brain.

In contemporary explanations of CE, there is an emphasis on brain regions, particularly those playing fundamental roles in producing motor output like M1, and their interhemispheric (i.e., local) projections. This emphasis can be traced back to the influence of the "cross-activation" hypothesis proposed by Parlow and Kinsbourne (1989) (Figure 2, adapted from[63]). This model incorporates the concept that unimanual motor commands from the active hemisphere are transmitted via cortical projections to the contralateral hemisphere, where these projections terminate in the spinal motor nuclei controlling the trained limb's muscles. Simultaneously, functional adaptations manifest in the motor circuits of the resting hemisphere, enhancing the motor capacity of the untrained limb. These adaptations are mediated by transcallosal projections from the active hemisphere. In other words, repeated unilateral movements induce parallel adaptations in the motor circuits controlling both sides of the body, ultimately enhancing the motor capacity of both the trained and untrained limbs.

This phenomenon has been primarily studied in the upper limbs, where voluntary contraction of one limb is thought to increase the motor evoked potential (MEP) amplitude in the resting contralateral limb$^{\text{ç}}$. In Muellbacher et al.'s study, MEP amplitude increased by 50% during 60% MVC, by 150% during 80% MVC, and by 300% during 100% MVC. While this experiment suggested an exponential increase in MEP with muscle contraction intensity, another study reported a linear increase in MEP amplitude during 30%-70% MVC muscle contractions[64]. Conversely, low-level muscle contractions at approximately 10% MVC are insufficient to induce cross-activation[55]. The 30% MVC threshold for inducing cross-activation was later confirmed by several experiments, showing significant MEP amplitude increases only at 30%-40% MVC or higher[65].

Interestingly, MEP amplitude increases induced by unilateral voluntary contraction are asymmetrical, displaying a lateralization effect in right-handed individuals but not in left-handed individuals. For right-handed individuals, cross-activation is more evident when the left non-dominant M1 is active but less evident when the right dominant M1 is active. This might reflect stronger inhibitory influences from the dominant to the non-dominant hemisphere in right-handers. In contrast, left-handers do not show such pronounced CE effects between the hemispheres, suggesting more symmetrical motor generation between the motor cortices[66]. Although most research focuses on the upper limbs, CE has also been demonstrated in the lower limbs. For instance, MEP amplitude increases were measured in the resting rectus femoris during simultaneous 50% MVC contractions of the contralateral knee extensors, with amplitudes ranging from 66% to 96%, depending on stimulus intensity. In contrast, 25% MVC had no significant effect, failing to support similar cross-activation thresholds for the upper and lower limbs.

The activity in the cingulate motor area (CMA), part of the anterior cingulate cortex and considered a strategic entry point for voluntary movement systems influenced by limbic structures, is closely related to the effort required for motor tasks. Extensive CMA neuron activity is modulated during ipsilateral hand activity, consistent with findings that cross-facilitation is enhanced with increased effort or volition.

While most experimental research on CE focuses on homonymous motor pathways, CE has been found to be not entirely selective for homonymous regions. For example, in a study with 75% MVC of the right tibialis anterior, MEP amplitude recorded in the left flexor carpi radialis muscle increased by approximately 50%, albeit to a lesser extent than in the homonymous right muscle at 75% MVC[67]. Interestingly, the same research group investigated a reverse design, showing stronger CE benefits in the left rectus femoris when comparing the effects of contralateral hand flexor contractions[68]. This preliminary evidence suggests greater cross-activation induced by upper limb contractions.

In summary, the precise neurophysiological mechanisms underlying CE remain unclear and understudied. Much research has focused on interhemispheric inhibitory mechanisms, with fewer studies addressing excitatory mechanisms.

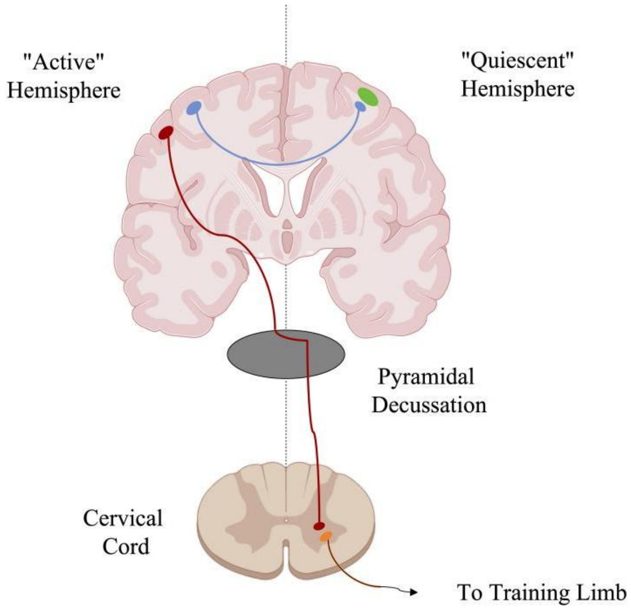

Figure 2. The conceptual model of "cross-activation"

4.3 Other Nodes in the Cortical Motor Network: The "bilateral-access" Mechanism

While the corticospinal projections from the M1 provide the principal means for the expression of CE , neural adaptations mediated by these projections may be instantiated in other brain centers[69, 70]. In this context, the potential role of non-primary motor areas, including the dorsal premotor area (PMd) and supplementary motor area (SMA), especially due to their extensive interhemispheric connections, has garnered particular attention[55, 70-72].

The long-held view posits that the neural adaptations underlying CE may be instantiated at one or more sites accessible by the motor networks controlling both sides of the body. This is the central tenet of the "bilateral-access" hypothesis[2, 4, 73]. The essence of this model is that unilateral experience refines "motor memories," which can be accessed by circuits in both hemispheres of the brain[74] (Figure 3). Repeated execution of unimanual motor commands by the motor cortex (MCx) of the active hemisphere leads to the activation of motor memories (e). These motor memories are expressed on a trajectory accessible by the motor networks controlling the effectors on both sides of the body. Blue solid arrows represent the ability of the motor circuits in the resting hemisphere to access motor memories when performing the trained actions with the untrained limb.

Nadel and Buresova's scheme has been described as a hypothetical extension[69], requiring motor memories to be encoded to the contralateral hemisphere of the trained limb, retrieved during the "read-out" phase when performing the trained actions with the untrained limb (Figure 4). Figure (A) illustrates the "read-out" phase, where motor memories in the active hemisphere are activated following the repeated execution of unimanual actions by the trained limb. When the untrained limb performs the same actions, the motor circuits of the resting hemisphere access these memories via transcallosal pathways. Figure (B) shows the subsequent "write-in" phase, during which repeated performance of the trained actions by the untrained limb results in the expression of motor memories in the resting hemisphere, adapted from[69]. This model is based on the phenomenon referred to as "transcallosal tutoring"[2, 73, 75].

We will consider specific brain regions constituting the cortical motor network, excluding M1, and their potential roles in mediating the adaptations underlying CE expression. The overall focus is on estimating intrachortical and interhemispheric connectivity using electrophysiological and neuroimaging methods. We exclude studies based on repetitive TMS interference, which primarily focus on the role of SMA, such as[55, 72]. It is estimated that using a standard coil for TMS at 120% of the resting motor threshold may activate an area spanning several square centimeters and one to two gyri[76]. Given that the SMA and its homologue are separated by the narrow longitudinal fissure, unilateral excitation of the SMA seems unlikely to be guaranteed in interference studies.

To explain the mechanisms of CE, many believe that the neuroplastic changes occurring during unilateral training can be utilized when the untrained limb is used. Contrary to the cross-activation model, task- and effector-specific changes in the state of neural circuits projecting to the muscles of the resting limb are not necessarily anticipated during training. The integrity of any such distinction necessarily relies on tools for delineating brain regions responsible for functions related to movements performed by one side of the body but not the other. As emphasized earlier, it is not even clear whether the primary motor cortex can be classified in this way.

Although proponents of the "bilateral pathways" emphasize the role of the corpus callosum as a means of information transfer from a single hemisphere, such bilateralization is not necessarily a logical imperative. The possibility of a bilateral representation of unilaterally acquired abilities cannot be excluded purely on a priori grounds. This possibility also highlights that "write-in" of transcallosal memory traces might involve an active process in the trained hemisphere, facilitating the flow of information in the opposite direction, i.e., from the trained to the untrained hemisphere. Through active "read-out," this can occur within just a few or even a single trial, forming a reiterated "motor memory" in the untrained hemisphere—a mode of command transfer that does not require direct "write-in" of equally active process-lateralized memory traces, designated as facultative transfer.

Therefore, the relationship between neural activity patterns that enhance performance during training and their subsequent emergence in the untrained limb's performance is an empirical question. We see little reason to distinguish "cross-activation" and "bilateral pathways" models on this basis. Instead, we propose that the degree of bilateral participation of various elements in the motor network and the CE benefits elicited by unilateral resistance training depend on the specifics of the training regimen.

In some experiments, participants are asked to repeat an action as many times as possible within a fixed interval or to repeatedly respond to a fixed stimulus in a reaction time task, which is not usually explicitly stated[77]. Learning is inferred from reduced reaction times, which correspond to the probability of transitions between successive stimuli in the control sequence while nominally maintaining constant demand-related requirements. This means there is no explicit requirement to increase the force or speed of keypresses or button presses. Thus, since these tasks are usually assumed to minimally engage motor execution, their performance improvements are typically interpreted as evidence of motor sequence learning.

Interhemispheric structural connections within the cortical motor network extend far beyond M1, although most known direct corticospinal projections originate from M1[78, 79]. Nevertheless, in a few instances, researchers have attempted to examine the functional contributions of these regions to CE . In these instances, the observed magnitude of behavioral changes rarely correlates with derived indices of brain structure/function[70]. Consequently, little is currently known about the potential functional contributions of non-primary motor areas in mediating the neural adaptations underlying CE. As a future research direction, it is worth further investigating how the functional integrity of this axis affects the overall quality of motor learning, particularly the extent of CE.

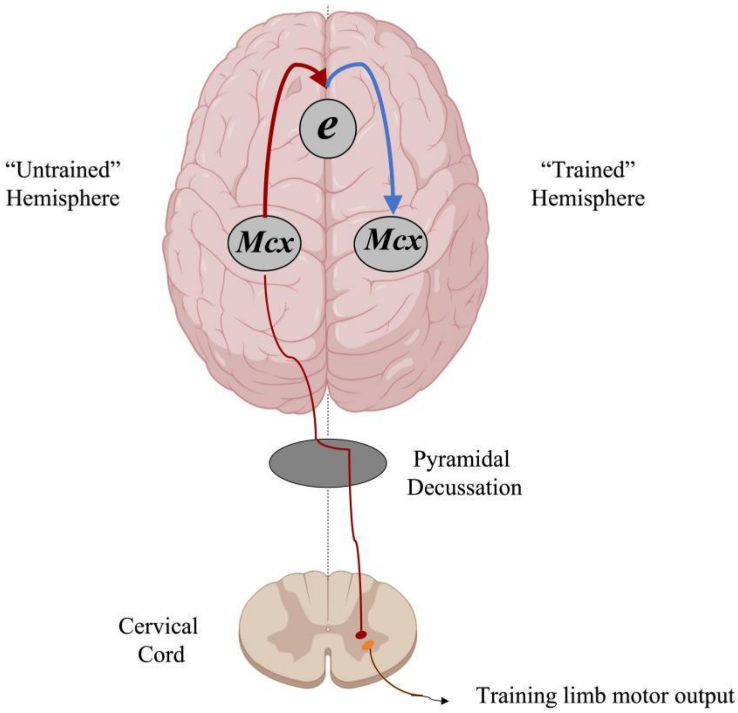

Figure 3. The conceptual model of "bilateral-access

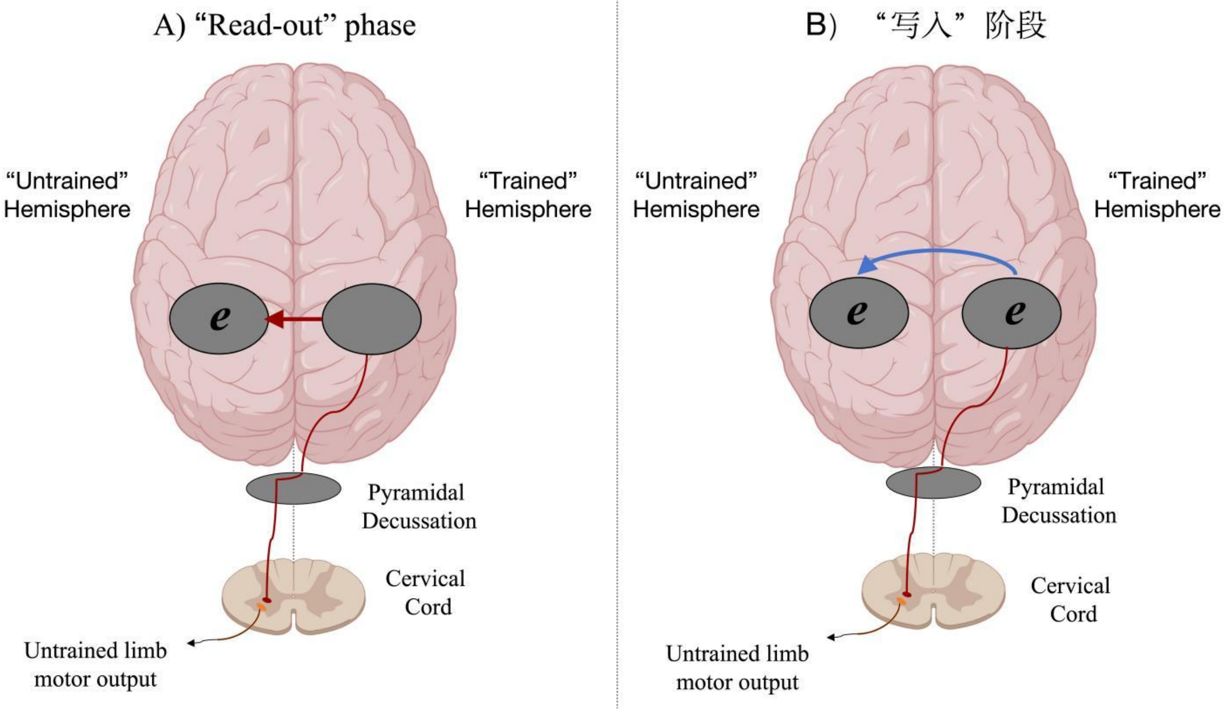

Figure 4. The two-stage concept model of "bilateral-access"

5. Clinical Rehabilitation Intervention Prescription

An analysis of Table 2 revealed a moderate to strong positive correlation between strength gains in the ipsilateral and contralateral limbs, confirming that the extent of contralateral strength gains largely depends on the gains achieved in the ipsilateral limb. Training distal muscle groups, regardless of body region, did not show different CE effects.

However, when comparing distal and proximal muscle groups by body region (i.e., upper or lower limbs), a greater increase in contralateral muscle strength was observed for distal muscles only in the upper limbs. Quantitative analysis showed CE benefits of 24% and 31% for upper and lower limbs, respectively, which are higher than the CE effect magnitudes of 9.4% and 16.4% reported in a previous meta-analysis by Manca et al. (31 studies, 785 subjects)[80]. Evidence indicates no difference in the occurrence of CE between young and elderly individuals[81-83], consistent with previous research[5], as observed CE effect sizes did not significantly differ between upper and lower limbs.

Regarding the impact of contraction type on CE benefits, eccentric contractions were found to be far superior to concentric, isometric, and super-maximal contractions. However, due to the limited number of studies on eccentric (n = 4; 94 subjects), concentric (n = 3; 9 subjects), and isometric (n = 4; 95 subjects) contractions, these findings, though significant, should be interpreted with caution, necessitating further systematic and comprehensive research. In terms of the intensity's impact on CE benefits, current theoretical mechanisms suggest that low-load experiments, due to the type of muscle fibers recruited and the specificity of the movement, result in negligible strength improvements and are prone to causing fatigue. In long-duration high-intensity contractions, the increased excitability of motor units in the trained muscle compensates for decreased muscle efficiency, leading to increased motor neuron recruitment. Previous studies have shown conflicting results regarding whether training the contralateral muscle to fatigue enhances CE benefits[5, 84-86]. The fatigue level and intensity of the training limb are crucial factors determining the presence and magnitude of associated electromyographic (EMG) activity in the contralateral homonymous muscle, which likely results from increased M1 cross-activation. Consequently, contractions leading to muscle fatigue or near fatigue not only increase associated EMG activity but also enhance M1 activation. According to the cross-activation hypothesis, the higher the simultaneous activation of M1 and the contralateral motor cortex during fatigue contractions, the better the training stimulus for increasing M1 excitability and CE, though the safety and reliability of inducing muscle fatigue in clinical rehabilitation must be considered.

From the included studies, five emphasized that participants had training experience, while 12 highlighted that they did not. We found that untrained subjects obtained significantly higher CE benefits compared to trained individuals, suggesting that in clinical rehabilitation, the generalizability of CE may need further consideration. Patients could be divided into those with sports injuries and those with vulnerable areas in middle-aged and elderly populations, with the latter potentially benefiting more from CE in their rehabilitation. This might be due to the neural mechanisms, as trained individuals likely have higher thresholds for neural stimulation, hindering optimal CE benefits from unilateral resistance training, a hypothesis that requires further investigation.When examining the impact of gender on CE benefits, we found that males had significantly higher effect sizes than females. This might be because males can endure higher training loads during intervention experiments, thereby increasing M1 activation, enhancing neural control over muscles, and improving CE benefits. However, the number and sample size of studies involving only female participants were insufficient (n = 3; 91 subjects), and the validity of this conclusion requires further consideration.

The aim of this chapter is to infer which unilateral strength training prescriptions (time, frequency, load intensity, and contraction type) can optimize strength gains in the untrained limb and to verify whether factors such as gender, body region, and health level influence CE benefits. Results indicate that unilateral resistance training can effectively increase muscle strength in the contralateral homonymous limb for both upper and lower limbs. Eccentric and isometric contractions are the most effective contraction types, with super-maximal contractions generally producing significant CE benefits, while concentric contractions require further research to establish their efficacy. Regarding load intensity, effect size is positively correlated with intensity, with only high-intensity exercises providing sufficient stimulation to increase muscle strength in the contralateral homonymous limb through neural mechanisms. Subjects with training experience may find it challenging to achieve significant CE benefits, potentially due to their elevated thresholds for neural stimulation from long-term resistance training, necessitating further research into the specific mechanisms and reasons. Training experience may hinder the acquisition of CE benefits, possibly due to long-term training effects. Finally, limited data suggest that gender might not be a limiting factor for CE benefits, though males achieve significantly higher CE training benefits, potentially due to their ability to endure higher load intensities during unilateral resistance training.

Table 2 Intervention measures targeting healthy populations

Study	Participants				Intervene				
	Training experience	Age	Male（n）	Female（n）	Body parts	Time/ week	Frequency/ time/week	Contraction form	Strength/RM
Manca et al., 2015	\	26.7±4.6	21	9	Dorsiflexor muscle of ankle	4	4	Concentric	4/6
Othman et al., 2020	\	10-13	43	0	Knee extensor muscle, knee flexor muscle, elbow flexor muscle	8	3	Plyometric	6-10
Magnus et al., 2014	Y	50.0±9.0	11	12	Supraspinatus, deltoid muscles	4	3	Plyometric	10-15
Poveda et al., 2021	Y	21.8±2.4	42	0	Knee	4	4	Concentric	25%/75%
Kidgel et al., 2015	N	～26	15	12	Wrist flexor muscle	4	3	Eccentric /concentric	6-8
Teixeira et al., 2023	\	～63	0	24	Lower limbs	4	2	Plyometric	70%-85%
Pelet et al., 2021	N	19-41	24	26	Elbow	4	3	Plyometric	40%/80%
Martinez et al., 2021	N	～21	36	0	Lateral thigh muscle	6	3	Eccentric	6-8
Munn et al., 2005	N	20.6±0.6	21	94	Flexor muscle of elbow	6	3	Plyometric	6-8
Farthing et al., 2003	N	～21	13	23	Arm	8	3	Eccentric	8
Farthing et al., 2005	N	20.8±0.4	0	39	Arm	6	4	Isometric	8
Weir et al., 1995	Y	23.7±2.6	17	0	Quadriceps femoris	8	3	Eccentric	80%
Farin˜as et al., 2019	Y	21-38	23	12	The biceps brachii	5	2	Plyometric	10
Farin˜as et al., 2023	Y	23±2	29	6	Knee	5	2	Plyometric	10
Beyer et al., 2015	N	18-31	17	0	Lower limbs	4	3	Plyometric	80%
Lee et al., 2009	N	18-24	13	7	Wrist	4	3	Isometric	10
Leung et al., 2018	N	26.4±6.9	21	22	Arm	4	3	Plyometric	80%
Lagerquist et al., 2006	\	21-42	6	10	Lower limbs	5	3	Isometric	8
Maroto-Izquierdo et al., 2021	Y	～22	40	0	Lower limbs	6	2	Plyometric	7
Coombs et al., 2016	N	18-36	11	12	Arm	9	9	Plyometric	70%
Haijun Yu et al.,	N	21±1.7	30	0	Right tibialis anterior	6	3	Isometric	60%-70%

2008					muscle				
Yan Qi et al., 2015	N	～23	0	20	Arm	6	4	Plyometric	8

Include literature sources: [9, 84-102]

6. Conclusion and Future Directions

The phenomenon of CE can be induced through various training methods such as voluntary contractions, muscle electrical stimulation, acupuncture at specific points, and motor imagery. Currently, CE is widely applied in clinical and rehabilitation treatments. Its principles and techniques are used in orthopedic rehabilitation for unilateral limb injuries and in the rehabilitation of hemiplegia following stroke or brain injury, yielding significant therapeutic effects.

In attempting to explain this adaptive mechanism, two theoretical hypotheses are currently proposed, both of which are compatible and aim to explain the occurrence of neural adaptation mechanisms. The "cross-activation" model suggests that adaptations to unilateral exercise extend to the other side of the body. The "bilateral-access" model posits that the motor patterns of unilateral activities are replicated on the opposite side by attempting the same tasks.

When developing clinical CE prescriptions, factors such as the patient's gender and training experience need to be considered. Male and inexperienced patients appear to benefit more significantly from CE. It is recommended to choose high-intensity (6-12 RM) eccentric unilateral resistance training as the rehabilitation exercise. The training cycle should ideally exceed four weeks, with intervals of 1-2 days, and each intervention should include 2-3 minutes of rest between sets to allow sufficient recovery time, preventing neuromuscular fatigue, and enhancing CE benefits. This approach aims to expedite and optimize the patient's rehabilitation process.

Future research should focus on the in-depth study of CE mechanisms, further exploration of its characteristics, and the investigation of its application scope to maximize the benefits of CE. By doing so, the CE concept can be better applied in rehabilitation and clinical settings.

Author'scontribution: Conceptualization: Liang Sun; methodology: Yi Wang; check: Jiong Luo; investigation:Lanfang Luo; resources: Yi Yang; datacuration: Qiushui Wangchuan; writing–roughpreparation:Liang Sun; writing–reviewandediting:Jiong Luo; visualization:Liang Sun; supervision: Jiong Luo; projectadministration:Jiong Luo.

All authors have read and agreed with the published version of the manuscript.

Funding statement: This study did not receive any external funding.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: Not applicable.

Conflicts of interest statement: The authors declare no conflicts of interest.

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