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Cross-education: Is it a viable method for rehabilitation?

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ABBREVIATIONS

MS	Multiple sclerosis
RCT	Randomized controlled trial

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In 1894, psychologists Edward W. Scripture, Theodate L. Smith, and Emily M. Brown reported for the first time the curious observation that practicing a motor skill with one hand also dramatically improved the non-practiced hand, giving rise to the phenomenon now coined as *cross-education*. Cross-education is the increase in motor output (i.e., force generation, skill) of the opposite, untrained limb following a period of unilateral motor training.[1] The potential to exploit such inter-limb adaptations for the purposes of rehabilitation of unilateral neurological or orthopedic injuries has captured the attention of scientists and therapists for years.

The magnitude of cross-education varies greatly between muscles and participants. In healthy adults, resistance training improves maximal voluntary force of the untrained limb by up to ~20%, usually half of the trained limb's improvement, but mirror training,[2] non-invasive brain stimulation[3] and neuromuscular electrical stimulation[4] can augment the transfer effects. Although not completely unraveled, researchers agree that the effects are likely driven by neuroplasticity in the primary and supplementary motor brain regions.[1]

Until recently, it has remained unclear if cross-education could aid rehabilitation of patients after a (unilateral) fracture, surgical intervention, a stroke, or multiple sclerosis (MS). During experimental arm immobilization of healthy adults, cross-education offset declines in strength and muscle cross-sectional area.[5] Cross-education appears to be amplified in clinical settings, with evidence for improved grip strength and range of motion after wrist fracture,[6] wrist and ankle strength in chronic post-stroke hemiparesis,[7] and ankle strength and mobility in persons with MS.[8] Cross-education effects in MS were similar to direct training of the more affected side;[8] efficacious for scenarios where the more affected limb is unable to train or becomes fatigued.

Still, caution is needed in interpreting these data because the promising clinical studies have small samples,[6,7,8] or lack a control or 'standard of care' comparison in a randomized controlled trial (RCT) design,[7] do not show persistent effects at six months follow-up,[5,8] or do not consistently show benefits beyond standard care for clinical-oriented outcomes.[6,8] The largest RCT involving cross-education as an adjuvant post knee surgery rehabilitation intervention reported no effects beyond standard care for neuromuscular or functional assessments.[9]

One hypothesis is that contraction history of the muscle influences inter-limb outcomes after unilateral training, where improvements in the untrained muscles following high-intensity strength training of the contralateral limb exceed gains from low-load direct training of a limb. Cross-education may be lessened when both limbs are trained because the local contraction history of the muscle inhibits potential signaling from the opposite limb motor pathway.[10] Cross-education could be best applied clinically in isolation, and not in combination with affected limb therapy - especially if it involves low load functional movement.

Amidst the limited evidence from large RCTs, can we say that cross-education is a viable method of rehabilitation? Indeed, most clinical studies are positive, and critically, none report negative outcomes. The risks of cross-education were based on the premise that it can worsen inter-limb asymmetry and exacerbate neglect of an impaired limb. But clinical studies so far suggest upper limb asymmetry was in fact reduced by cross-education[6,7] and lower limb asymmetry was not worsened.[7,9] Clinical emphasis on avoiding asymmetry may be short-sighted because it diverts focus from the absolute functional capacity of the impaired limb. If clinical function of the impaired limb is improved, and neuromuscular activation yields movements that before were not possible,[7] the risk of enhancing asymmetry should be a secondary concern[1] that can be addressed by direct exercise once functional ability is restored. Caution is important where we lack clinical data on cross-education effects (e.g., acute and sub-acute stroke). Training the unaffected limb is somewhat incompatible with the widely used constraint-induced movement therapy, and the techniques are yet to be studied in conjunction. Perhaps the two are antithetical and target different patients. The evidence suggests cross-education is most usefully applied when the impaired or injured limb is very weak, immobilized, or unable to function unaided, whereas ideal candidates to constraint-induced movement therapy must have a minimum functional reservoir in order to benefit. Future studies need to assess whether adding cross-education prior to direct training is functionally and clinically relevant.

We suggest that contralateral training stimulates neuroplasticity in motor pathways of the injured or impaired side, serving to offset weakness and wasting and stimulate recovery after orthopedic injury or neurological impairment, or diminish effects of neurological disease. The possible implications of cross-education for management of contralateral musculoskeletal pain seem promising but require further investigation. Importantly, we lack evidence from large RCTs that explore the combination of cross-education with mirror training, electrical stimulation, and non-invasive brain stimulation. We endorse collaborative efforts for clinical studies to explore these novel avenues as we deepen our understanding of benefits and limitations of cross-education as a rehabilitation method.

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