Explaining the cortical and spinal mechanisms of cross-education in humans.

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Primary objective: To determine if unilateral exercise with the use of a mirror produces greater adaptations in the untrained limb than exercise without a mirror. Secondary objective: To determine corticospinal and cortical mechanisms of adaptations...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39555

Source
ToetsingOnline

Brief title
Corticospinal cross-education mechanisms

Condition

- Other condition

Synonym
one sided physical contstraints, Unilateral injuries

Health condition

Unilaterale letsels

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cross-education, H-reflex, Mirror training, Transcranial magnetic stimulation (TMS)

Outcome measures

Primary outcome

Primary outcome measure is the gain in maximal voluntary muscle strength of the untrained wrist flexor muscle group.

Secondary outcome

Secondary outcome measures are, in the left and right wrist flexors, the size of the magnetic brain stimulation produced motor evoked potentials (MEPs), size of the short-interval intracortical inhibition (SICI), size of the maximal compound size of the maximal spinal reflex (M wave) and the size of the spinal excitability, H reflex. MEPs measure corticospinal excitability.

SICI is the inhibition of the test MEP when the suprathreshold TMS pulse (the test stimulus) is preceded by a few milliseconds with a subthreshold TMS pulse (the conditioning stimulus) and it is a measure of motor cortical inhibition, and can thus be used to examine cortical influences. The Hmax/Mmax ratio, on the contrary, is a measure of the spinal influences.

To address spatial specificity of XED, we also test the force of the left index finger, using a custom built dynamometer (7, 8).

Note: Reference numbers correspond with the reference number used in the

research protocol.

Study description

Background summary

Patients with a certain neurological (stroke) or orthopedic condition (wrist fracture) could benefit from faster recovery of lost function in the involved limb. There is emerging evidence to suggest that intensive motor practice with muscles of one limb improves motor function of the homologous muscles in the other limb, a phenomenon called cross-education (XED) (1, 4, 19). Meta analyses suggest that the magnitude of transfer is about ~10% and the highest from the right-dominant to non-dominant limb in both men and women (12). The most often measured outcome is maximal voluntary force. Imaging and TMS studies suggest that the mechanism of transfer is related to the reorganization and enlargement of activation areas of the brain involved in the unilateral contraction and in particular, modulation of interhemispheric inhibition via the corpus callosum (3, 6, 8, 9). Recent studies also showed that XED can reduce the strength loss produced by immobilization of healthy subjects* wrist (3), suggesting that the XED-produced changes in voluntary muscle force are clinically meaningful.

A parallel neurological observation is the anatomical existence of the mirror-neuron system and its functional role in motor rehabilitation. The mirror-neuron system consists of neurons in the occipital, temporal, and parietal visual areas and the two frontoparietal motor areas (10, 15). Mirror neurons discharge action potentials when someone performs a specific motor action and also when someone observes another individual performing a similar motor action (5, 15). There is a growing suspicion that the mirror-neuron system is involved in XED but this idea has not been tested.

A new form for inducing XED would include mirror therapy. The idea of mirror therapy is that the mirror reflection of the training hand is superimposed over the untrained hand (11, 13). In other words, when a volunteer performs a hand grip and sees at the same time the mirror of image of this right hand in a mirror as if it were the left hand, the notion evolves that the person sees the left hand exercising. The fake view of the exercising left hand activates elements of the mirror neuron system, and this activity, we hypothesize, augments the transfer compared with practice that uses no mirror. Mirror therapy has been used to help stroke patients with motor skill learning and also in patients with phantom pain (17, 18) but none of these studies used the idea to strengthen muscles and capitalize on the combination of mirror therapy with XED.

In the present study participants will perform 18 session of isometric handgrip contractions with the dominant right hand. Participant were randomly allocated to three different groups. The mirror therapy group performed handgrip contractions while viewing the exercising hand in the mirror, the XED group performed handgrip contractions while viewing the non-exercising left hand, and the third group is the non-exercising control group. Main outcome measure is the maximal voluntary force of the left and right wrist flexors. The secondary outcome measures are, in the left and right wrist flexors, the size of the transcranial magnetic brain stimulation (TMS) produced motor evoked potentials (MEPs), size of the short-interval intracortical inhibition (SICI), size of the maximal compound size of the maximal spinal reflex (M-wave) and the size of the spinal excitability, H-reflex. MEPs measure corticospinal excitability. SICI is the inhibition of the test MEP when a sub-threshold conditioning TMS pulse precedes by a few milliseconds a supra-threshold TMS test pulse. SICI is a measure of motor cortical inhibition and can examine cortical influences. The Hmax/Mmax ratio, on the contrary, is a measure of the spinal influences.

We will address the following questions:
1. Does unilateral exercise with the use of a mirror produce greater adaptations in the untrained limb than exercise without a mirror?
2. Are the gains in muscle strength associated with changes in corticospinal and cortical excitability measured in elements of the mirror-neuron system using TMS?
3. Are the changes in force (behavior) and excitability (mechanism) specific to the trained muscle group (spatial specificity)?
4. Do the changes outlast the duration of the training period for a month after the end of the training program?

Our main expectation is that chronic unilateral gripping exercise with the use of a mirror produces larger adaptations in the untrained target muscle than exercise without a mirror in healthy young men and women.

Note: Reference numbers correspond with the reference number used in the research protocol.

Study objective

Primary objective: To determine if unilateral exercise with the use of a mirror produces greater adaptations in the untrained limb than exercise without a mirror.

Secondary objective: To determine corticospinal and cortical mechanisms of adaptations to unilateral exercise with and without the use of a mirror.

Study design

This research project is a randomized clinical trial study with an open and parallel design. This study contains three different groups and the subjects are randomly assigned to one of three groups. Subjects will exercise the right hand because the transfer is the biggest to the left hand when right-handed individuals exercise the dominant right-hand (2).

Maximal one week before the start of the exercise program subjects will perform the pre-test and maximal one week after the end of the exercise program they will perform the post-test. Four weeks after the end of the exercise program the follow-up measurement will be performed.

Note: Reference numbers correspond with the reference number used in the research protocol.

Intervention

Two groups (groups 1 and 2) will exercise three times per week, six week long. Subject assigned to the third group will not exercise. Groups 1 and 2 will perform isometric handgrip contractions of the right hand. The training program will be completed using the handgrip dynamometer (JAMAR) in the same fashion as for testing (seated position) and is supervised at all times. This was done to ensure specificity between the strength training and the strength testing task. The program was progressive in nature, beginning with three sets of eight repetitions and increasing in volume by one additional set each training day, up to a maximum training volume of six sets of eight repetitions. The training program included a taper down to two sets of eight repetitions for the last training session. The isometric repetitions were 3 seconds long and were cadenced using a metronome. Participants were given feedback regarding the force achieved during the repetitions and were given verbal encouragement. During unilateral training, participants were reminded to completely relax the non-exercising left arm. The program consisted of 18 training sessions in total.

Group 1, XED group: exercise the right wrist and looking at the left hand with a view of the right hand blocked.

Group 2, Mirror group: exercise the right hand with a view of the right hand in the mirror with view of the right hand blocked.

Group 3, Control group: Subjects attend the same number of sessions as groups 1 and 2, grasp the dynamometer but do not exercise. They look at the left hand with a view of the right hand blocked.

Study burden and risks

Participant will visit the Center for Human Movement Sciences three times per week for performing the exercise sessions, and also the control group will

visit the Center for Human Movement Sciences. Every training session will last for 15 minutes. In total, the subjects will visit the Center for Human Movement Sciences 18 times. There were no risks for participating in the strength training program and the load for the joints and limbs is very low. Furthermore, the training load for the exercising limb is build up gradually and therefore overtraining will not occur.
Subject have to visit the Center for Human Movement Sciences three times extra for performing the pre-test, post-test, and follow-up. The measurements will be identical in all three tests. One testing session will last for maximal 1.5 hours, in which they will have to seat for most of the time. Resting periods of 2-3 minutes are given if needed. A longer resting period of 10 minutes is built in between the TMS and H-reflex data collection.

Participation in this study comprises electrical stimulation of the medial nerve and magnetic stimulation of the motor cortex during the performance of submaximal isometric contractions of the wrist. The TMS may cause slight discomfort lasting less than a second on the scalp near the coil. It may also cause some twitching of the muscles, the face and jaw, which may be unpleasant and surprising but not painful. Peripheral nerve stimulation causes the muscles to twitch that can be more surprising than painful. It can cause some momentary burning and tingling sensation. There are no known long-term risks of peripheral nerve or magnetic brain stimulation. Electromyography (EMG) of the flexor carpi ulnaris and extensor carpi ulnaris muscles will be recorded. Therefore the skin underneath the three electrodes will be shaved and cleaned. This may cause some light irritation of the skin.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy young adults, age 21 - 35 years, right-handed,

Exclusion criteria

(1) Neurological disorders
(2) Pro-epileptogenic medications or medications known to affect balance
(3) Epilepsy
(4) Any metal in the brain/skull
(5) Pregnancy or suspicion of pregnancy (self-reported)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	42
Type:	Anticipated

Ethics review

Approved WMO Date:	13-03-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL42356.042.13