Upper limb training after stroke (ULTRA-stroke): Contrasting the clinical effects and underlying mechanisms of unilateral and bilateral training

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Ethical review	Approved WMO
Status	Pending
Health condition type	Structural brain disorders
Study type	Interventional

Summary

ID

NL-OMON33953

Source
ToetsingOnline

Brief title
ULTRA-stroke

Condition

- Structural brain disorders

Synonym
CVA, stroke

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: arm training, bimanual, stroke, unimanual

Outcome measures

Primary outcome

The Action Research Arm Test (ARAT) serves as primary outcome measure. This is a valid, reliable, and responsive performance test (van der Lee et al., 2001) of the ability to perform gross movements and to grasp, move and release objects differing in size, weight and shape (Lyle, 1981). The minimal clinically important difference is set at about 10% of the scale*s range, i.e. 6 points (Van der Lee et al., 1999); improvement by > 10 points is defined as return of dexterity (Kwakkel et al., 2003).

Secondary outcome

Clinimetrics:

Secondary outcome measures; detecting confounders, comparing groups, and tracing changes per patient in time:

Motricity Index (MI):

Fugl-Meyer arm/hand test (FM)-arm:

Nine Hole Peg Test (NHPT):

The Nine Hole Peg Test (NHPT) is a reliable and valid test that measures manual dexterity (Mathiowetz et al, 1985; Heller Erasmus MC modification of the (revised) Nottingham Sensory Assessment (EmNSA):

Motor Activity Log (MAL):

Stroke Impact Scale (SIS):

Peripheral stiffness:

Methods: Endpoint mechanical behavior, resulting from a mix of visco-elastic (intrinsic) and proprioceptive reflex (reflexive) properties, will be assessed under both passive and active conditions using a haptic robot for the wrist (*Wrist-analyzer*, Moog FCS Inc). This powerful, force-controlled manipulator applies quasi-random variations of the net moment of force over a wide range of frequencies, as well as controlled force perturbations. Surface EMG is measured for additional validation.

Interlimb interactions:

Methods: Ridderikhoff et al. (2005) developed a methodology that dissociates between the contributions of three sources of interlimb interaction: 1) integration of feedforward control signals to both hands; 2) error correction of the phasing between the hands, based on afferent signals; 3) (unintended) phase entrainment by contralateral afferent signals, probably resulting from spinal reflexes. It is based on systematic comparisons between four coordination tasks involving bimanual performance (in- and antiphase coordination) or unimanual performance with or without comparable motor-driven movements of the contralateral hand: (a) unimanual rhythmic coordination with an auditory pacing signal (UN); (b) idem, while the contralateral hand is moved passively with a phase shift of 30º with respect to the required movements of the active hand (UNm); (c) kinesthetic tracking (KT): unimanual active movements are to be coordinated (in- or antiphase) with the passive rhythmic movements of the contralateral hand (identical to those used in [b]); (d)

active auditorily-paced bimanual coordination (in- or antiphase; AB). This method, with minor modifications, is applied in the proposed study. The tasks are performed in an experimental set-up in which passive movements can be imposed using a servo-motor and the active movements are measured using potentiometers. All tasks are performed at the movement frequency at which the subject can comfortably perform the antiphase pattern in the first test session (pretest). Depending on the task conditions, the motor-driven, passive movements are based on either the movements of the to-be-moved hand as recorded during condition (d), which is therefore the first task to be performed, or a predefined sinusoidal pattern (with added random noise). Given the inherent functional asymmetry in the subjects, tasks (a)-(c) are performed with both the paretic and the non-paretic hand as active hand (order counterbalanced over subjects; yielding 2 sessions of 1 hour each). For the associated analyses, see Ridderikhoff et al. (2005). Surface EMG is measured for additional validation.

Brain dynamics:
Methods: All subjects perform simple unimanual and bimanual isometric force production tasks with their fingers, while whole-head magneto-encephalographic (MEG) recordings are made. Task performance (onset and displacement) is monitored by a self-produced device measuring the strain gauge.

Study description

Background summary

In the Netherlands, each year more than 32,000 patients sustain a stroke (Loor et al., 1999) and the incidence is expected to have increased by 30*45% in 2015 (Ruwaard & Kramers, 1997). About 80% of the survivors have an upper limb paresis immediately after stroke (Nakayama et al, 1994), hampering movement of the paretic arm and bimanual coordination (Ustinova et al., 2006). Unfortunately, with conventional treatment programs only one third of all stroke patients regain some dexterity within 6 months post-stroke (Dobkin et al., 2005). However, recent studies have revealed promising results with specific interventions aimed at arm-function improvement.
One such intervention is bilateral arm training with rhythmic auditory cues (BATRAC), which has been shown to have beneficial effects on the paretic arm (Whitall et al., 2000), possibly as a result of changes in contralesional cortical networks (Luft et al., 2004).
In contrast, various controlled trials have suggested that intensive unilateral training by constraining movements of the nonparetic arm (constrained-induced movement therapy; CIMT) is an effective method for improving upper limb function (Hakkenness & Keating 2005; Wolf et al., 2006). This suggests that training may also induce beneficial changes in the affected rather than nonaffected hemisphere and raises the question whether in BATRAC the improved functionality of the paretic arm indeed results from exploiting interhemispheric interactions, or merely from training with the affected arm (cf. Luft et al., 2004).
To address this question (cf. Rose & Winstein, 2005) the proposed project entails a randomized control trial (RCT) in which the expected merits of both BATRAC and CIMT are compared with those of an equally intensive (i.e., dose-matched) conventional treatment program (DMCT), while also the effects of BATRAC and CIMT are compared on several outcome measures. To this end, participants are divided over three intervention groups and the effects of the interventions are assessed (1) prior to training, (2) after 6 weeks of training, and (3) 6 weeks after training.

Study objective

The project has two principal aims: (1) to assess the relative effectiveness of the three interventions, also as a function of patient characteristics, and (2) to delineate the functional and neurophysiological changes that are associated with those intervention effects. To assess the effectiveness, a range of functional outcome measures will be determined pertaining to ADL functioning, motor ability of the paretic arm, bimanual coordination, and peripheral motor functioning. Besides shedding further light on the merits of bilateral versus unilateral upper limb training in general (Stewart et al., 2006), the study will generate specific insights into the effectiveness of distally oriented BATRAC, aimed at improving wrist and finger extension (Kwakkel & Kollen., 2007). In light of contrasting results and divergent perspectives on associated mechanisms (Richards et al., 2008), the potential dependence of the effectiveness of the interventions on neurological characteristics of stroke survivors will also be examined. To uncover the mechanisms associated with

therapy-induced functional improvement, two kinds of analysis are included. First, changes in three empirically identified (and functionally defined) sources of interlimb interaction will be examined. Specifically, BATRAC is expected to induce more improvement in these interactions than both CIMT and DMCT. Second, MEG recordings will be analysed to identify treatment-induced neuronal reorganizations. CIMT is expected to result primarily in changes in ipsilesional hemisphere functioning, which may be related to restitution of its former functionality. BATRAC, on the other hand, is expected to induce primarily adaptations in the contralesional hemisphere (Luft et al., 2004), which would indicate compensatory cortical reorganization in which the coupling to the nonaffected hemisphere gains a special role in the motor control of the paretic arm.
In short, the primary research questions are: 1) Is BATRAC or CIMT, when compared to DMCT, more effective in terms of recovery of (unimanual and bimanual) hand and arm function in subacute stroke patients? 2) How are the observed changes in functionality related to changes in peripheral stiffness, interlimb interactions and cortical inter- and intrahemispheric neural networks?

Study design

Patients will be placed in one of three intervention groups (BATRAC, CIMT, DMCT). Whereas the pretests (t0) are performed in the week prior to the intervention, posttests (t1) are performed in the week after the intervention. After the first assessment an intervention period will take place for 6 consecutive weeks, 3 times a week for 1 hour. The degrees to which changes are sustained are examined using retention tests (t2), 6 weeks after completion of the intervention.

Intervention

The interventions are applied by physiotherapists and/or occupational therapists working at the RCA. Where possible, interventions in groups is preferred (no more than 3 patients per group).
The BATRAC group receives 60-minute sessions, 3 days a week for 6 consecutive weeks. Treatment will be applied in 5-minute movement periods interspersed with 5-minute rest periods. The lower arms are fixated and the subject performs flexion and extension movements about the wrist in the horizontal plane, paced by an auditory metronome. The tempo of the auditory cues depends on the severity of upper limb deficit and is selected individually. Over the course of training the tempo is adjusted in response to improvement in task performance. The movements are performed in phase (simultaneous flexion or extension) and antiphase (flexion of one wrist coincides with extension of the other), where maximal flexion/extension should coincide with the auditory cue. Changes between the two modes are included to avoid loss of motivation.
The CIMT group receives 60 minutes of task-oriented training of the upper

extremity, aimed at improving dexterity of the paretic arm (i.e., shaping), 3 days a week for 6 consecutive weeks. Task difficulty is increased progressively using behavioural techniques of shaping and successive approximation (Taub et al., 1999). In addition, the Padded Safety Mitt (Samson Preston # 6727; Sammons Preston, Inc, Bolingbrook, IL, USA) is applied to immobilize the non-paretic arm for at least six waking hours each working day to prevent from the non-paretic arm taking over tasks of the paretic arm. The content and duration of the CIMT therapy as well as the shaping exercises are recorded in a patients* log reflecting the progress in reaching treatment goals.
Dose-matched control treatment (DMCT) consists of exercise therapy based on existing guidelines for exercise therapy as shown by Dutch Society of Occupational Therapy (NVE) and Royal Dutch Society of Physical Therapy (KNGF) (van Peppen et al, 2004). Therapy will be applied 60 minutes per treatment session, 3 days a week for 6 consecutive weeks and will not contain elements of the other two therapies. The content and duration of the sessions is recorded in patient logs.

Study burden and risks

We are aware of the burden on patients of intervention and (clinical) measurements. However, evidence is compelling that the functionality of the impaired paretic arm may be improved by using specific therapeutic interventions. Next to the opportunity to evaluate specific interventions for the paretic arm, we expect to find answers to fundamental research questions that are vital to our understanding of functional recovery after paresis of the upper limb. The proposed BATRACT-CIMT trial goes beyond testing the effectiveness of the interventions, by extending the analyses to the mechanisms of exercise-induced neuroplasticity that are associated with functional improvement (e.g., the importance of cortical reorganization in the affected and non-affected hemispheres and cerebellum for regaining dexterity).

Clinical assessments
Assessments of included patients for the trial are performed by questionnaires and (functional) tasks. There are no invasive measurements. Care is taken that the total time to perform all the required assessments is no more than 1 hour.

Peripheral stiffness assessment
Peripheral stiffness assessment involves the use of a haptic robot (Wristalyzer, Moog FCS INC) and EMG. The Wristalyzer is a one-degree-of-freedom wrist perturbator for neurological research and diagnostics. Surface EMG is measured for additional validation. Both methods are non-invasive and do not have any side effects. The assessment will take about 40 minutes (including mounting and demounting).

Interlimb interactions
At the Faculty of Human Movement Sciences at the Vrije Universiteit an apparatus is developed for the assessment of interlimb interactions. The

patient*s forearms will be fixated in a neutral position, whereas the hands, supported by horizontally movable manipulanda can be actively or passively moved around the wrist. The movement trajectory is determined by the patient*s own abilities. The method is not invasive and assessment is separated in two sessions, each no longer than 1 hour.

Brain dynamics
The neural effects of BATRAC and CIMT are assessed with MEG. With MEG, the brain can be observed *in action* without any of the risks associated with other imaging techniques. Surface EMG is used to monitor task performance. All patients perform simple unimanual and bimanual isometric force production tasks with their fingers. The assessment takes no longer than 1 hour.

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

First ever ischemic or hemorrhagic subacute stroke in one of the hemispheres, verified by CT and/or MRI;
upper limb deficit, yet able to execute 1) >10 dgrees extension/abduction of the thumb, 2) >10 degrees extension in two additional digits, 3) >10 degrees wrist extension; less than 53 points on the Action Research Arm Test; 18-80 years of age; motivated to participate; give written or oral informed consent

Exclusion criteria

Suffer from upper extremity orthopeadic limitations that may affect the results; not being able to communicate (<4 points on the Utrecht Commincation Observation); disoriented with regard to time and place (<24 points on the Mini Mental State Examination); pacemaker or other metalic implants (only for MEG)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2009
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO
Application type: First submission
Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 27945
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL20456.029.08
OMON	NL-OMON27945