The Challenges of Dynamic Balance & Gait for People after Stroke

Hanneke van Duijnhoven

DONDERS SERIES

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Chapter 1

General introduction and outline of the thesis

Introduction

Stroke

Worldwide, approximately 10 million persons sustain a stroke each year.[1] Due to aging and expansion of the population, the number of persons suffering from a stroke in the Netherlands is expected to increase from 186.000 in 2011 to 343.000 in 2040.[2] Over the years acute stroke care has improved and endovascular treatment for ischemic stroke has developed rapidly.[3, 4] This development will lead to a further increase in the number of stroke survivors and a larger population of persons with a stroke-related disability living in the community.[1] According to the definition of the World Health Organization, a stroke is a rapidly developed sign of focal (or global) disturbance of cerebral function lasting more than 24 hours with a vascular cause.[5] The most common location of a stroke is supratentorial, and ischemic strokes are approximately four times more prevalent than the haemorrhagic type.[4, 6]

Following a supratentorial stroke, acute neurological symptoms may present as cognitive, sensory and/or motor deficits. Symptoms in the cognitive domain can be focal, like aphasia and visuospatial hemineglect, or general, like reduced speed of information processing, memory disorders and behavioral problems.[6, 7] Somatosensory loss may affect the face, arm and leg, and can influence movement and consequently the learning of new skills after stroke.[6, 8] Motor impairments include hemiparesis, loss of motor selectivity, reduced motor speed, and increased muscle tone ('spasticity') of the affected extremities, while trunk control may be impaired as well. The pattern of motor deficits depends on the location of stroke. A hemiparesis contralateral to the affected hemisphere with equal involvement of the face, arm and leg can be seen when the internal capsule is involved.[6] When a stroke is located in the motor cortex the motor impairment is often more focal, with predominant involvement of the face and arm after an occlusion of the middle cerebral artery (the most frequent ischemic stroke localization) and predominant leg involvement after a anterior cerebral artery stroke.[6]

Although almost all survivors experience some kind of functional recovery in the first months post stroke, residual impairments often remain.[9] Spontaneous neurological recovery progresses the fastest in the first days to weeks after stroke and then plateaus after 3 to 6 months.[10, 11] The learning of new skills is the result of both neural repair (restitution of function) and the learning of new strategies to complete tasks which are hampered by motor impairments (substitution of function).[12] Restitution of function seems to be limited to the first 10 weeks after stroke[9], whereas improvements from 3 months onwards are more likely to be the result of substitution of function.[12] As a result of remaining impairments, people after stroke can experience problems with different kinds of activities in daily life and participation in the society. This varies from problems with essential indoor activities like dressing and washing, to diverse outdoor activities like walking, recreation and leisure.[10] In addition, social participation, like working and maintaining interpersonal relations, can be impaired.[10]

Falls after stroke

As a result of residual impairments, falls are a common phenomenon in the post-stroke population. Overall, fall incidence rates are 3-10 times higher than in the healthy elderly population.[13] The risk of falling varies across the post-stroke phases: 3.8-22.0% of the patients have fallen at least once in the acute care setting, 10.5-47.0% during inpatient rehabilitation, and 33-70% at one year follow-up.[14-17] Fall incidence rates, however, are considerably equal in the acute, sub acute and chronic phases after stroke (2.2-4.9, 1.3-6.5 and 1.4-5.0 falls each person year, respectively). Both in the hospital and in the inpatient rehabilitation setting, most falls occur nearby patients' bed and in the bathroom/toilet area.[13] The most commonly reported activity leading to a fall is transferring.[14] In contrast, walking is the most frequent activity leading to falls in community-dwelling stroke survivors, and the majority of these falls occur in the living room, bedroom or garden.[13, 14, 16]

Falls are of great clinical interest after stroke due to their consequences. Injuries after a fall vary from mild (e.g. soft tissue) injuries to severe injuries (e.g. fractures, head injury).[13, 16] Although fracture rates in the stroke population (0.6-8.5%) do not differ from the rates reported for healthy elderly, a fracture of the hip (particularly on the paretic side) is 3.8 to 2.1 times more likely to occur in people with stroke.[14] These hip fractures are particularly troublesome, because independent mobility after a fracture is

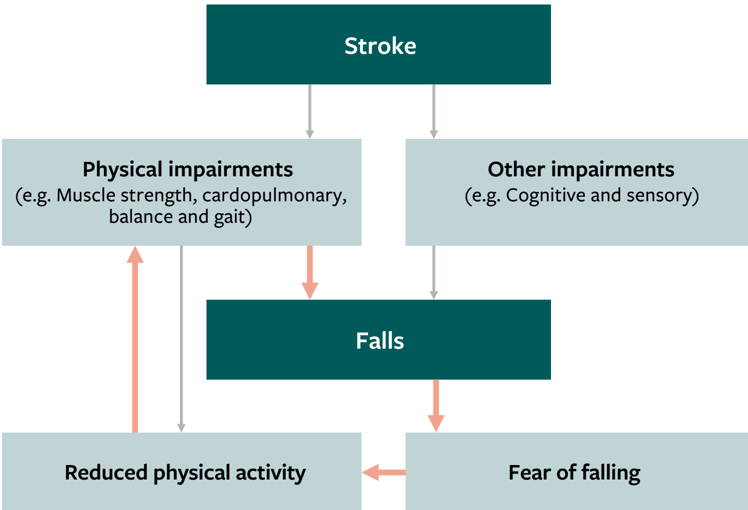

Figure 1 Interactions between risk factors, falls, and consequences of falls in persons with stroke.

Adapted from figure 1 originally published in *Weerdesteyn V, de Niet M, van Duijnhoven HJ, Geurts AC. Falls in indiviuals with stroke. J Rehabil Res Dev.2008;45(8): 1195-213.*

regained in only 38% of the people after stroke versus 69% in the general population.[14] Mortality rates are found to be doubled 3 months after surgically treated fractures in individuals with stroke (10% vs 5% in hip fracture patients without stroke).[14]

An additional complication after a fall is fear of falling, which is common after stroke with 88% of fallers reporting fear.[14] In fact, one study reported that fear of falling at one month post stroke was the best indicator for falling at 6 months.[18] Fear of falling often leads to reduced physical activity and subsequent deconditioning (e.g. loss of muscle mass, osteoporosis, reduced cardiopulmonary functions, depression)[15] and, consequently, to a further increase in fall risk (see figure 1).[14, 19] In this perspective, recurrent falls cause a vicious circle of fear and loss of physical and mental functions, leading to increased mortality (as indicated by the green arrows in figure 1).[14]

Previous studies have identified several risk factors for falls after stroke. These factors seem to be similar for all post-stroke phases. The most important risk factors are balance and gait deficits and ADL dependency.[13, 14, 20] Besides the obvious functional impact of hemiparesis on balance and gait capacity, some studies have suggested that a fall is more likely to occur when walking requires increased cognitive control.[14, 16] Persons with specific mental deficits,[13, 14, 21] such as hemineglect[13] and depression,[13, 14, 21] and those with severe sensory deficits[14], such as loss of proprioception, also seem to have an increased fall risk. In the following paragraph, the most important balance and gait deficits after stroke will be further elaborated.

Balance and gait deficits after stroke

Balance and gait deficits have received considerable attention in the literature as the most important risk factors for falls after stroke. As stated before, people after stroke can experience a multitude of sensorimotor impairments. These can lead to problems with maintaining balance and walking under both static and dynamic circumstances. In the following sections, I will provide a brief overview of the present knowledge on balance and gait deficits after supratentorial stroke.

Balance

Maintaining upright balance during sitting, standing or while moving (e.g. during reaching, bending over or walking) is a common, yet complex task of every-day life. It involves the interaction of several individual, task-specific and environmental factors, as previously conceptualized in the systems framework by Shumway-Cook and Woollacott (figure 2).[22] *Individual* factors include motor, sensory and cognitive functions. Postural *tasks* that we encounter in daily life are maintaining steady state, proactive and reactive balance control. Steady state balance control involves keeping the center of mass (CoM) within the base of support (BoS) under predictable and non-changing circumstances. Proactive balance control is the capacity to actively control balance in anticipation of voluntary movements that could be destabilizing, and reactive balance control is the capacity to restore balance after an unexpected perturbation. *Environmental* factors can influence the way we are able to use our sensory, cognitive and motor functions to control balance. Changes in the support surface require adaptations in the recruitment of muscles and forces needed to maintain balance. In addition, changes in sensory context through visual and surface manipulations influence the way we can use our sensory functions. Changes in cognitive load, e.g. performing multiple tasks at the same time, affect the way cognitive functions, like for instance attention, are able to influence balance control.

As already mentioned, a stroke can hamper motor, sensory and cognitive functions, leading to a diminished capacity to execute the different postural tasks. Sitting balance is generally impaired early after stroke and is an important goal of rehabilitation. Particularly in this phase, people show an asymmetrical sitting position due to a phenomenon called

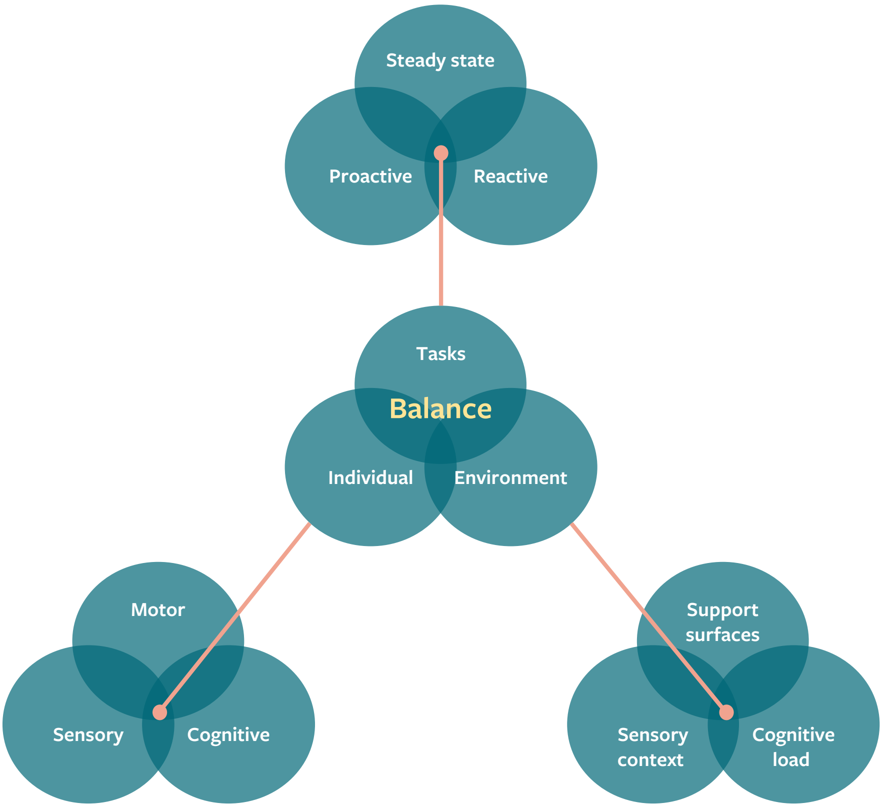

Figure 2 Systems framework: task-specific, individual and environmental factors influencing balance.

'lateropulsion'. Approximately 42 percent of people with hemispheric stroke actively tilt the body laterally towards the paretic side, due to an altered perception of verticality.[23, 24] In addition, under steady state conditions, people early after stroke tend to show increased trunk sway, which is more pronounced in the medio-lateral than in de antero-posterior direction.[25] Trunk sway increases further when people after stroke sit on an unstable surface and when vision is deprived.[25] The weight distribution while sitting still does not seem to differ from healthy controls.[26] The majority of recovery of trunk control occurs in the first four to six weeks after stroke[25] and shows a similar time course as the recovery of arm, leg and functional capacities.[27] Under more dynamic circumstances, people after stroke show more lateral displacement of the trunk when reaching forward (towards the opposite side of the reaching arm) and less lateral movement when reaching sideways to the unaffected side.[26] Overall, to date, not much is known about the movement patterns of such dynamic sitting balance tasks after stroke.

During steady state standing balance control, people early after stroke can show some lateropulsion, leading to an active 'lean' towards the affected side.[24] In addition, there is an increased body sway, particularly in the medio-lateral direction.[14] A change of the environment, e.g. with visual deprivation or the addition of a cognitive dual task, further increases imbalance during quiet stance. [14, 28] It therefore seems that standing balance control is not only influenced by motor functions, but by cognition as well. In the first weeks after stroke both the increased body sway and lateropulsion diminish gradually.[23, 28] A couple of weeks to months post stroke, however, people after stroke still show an increased reliance on the non-paretic lower limb, while standing quietly.[14, 28, 29] Several studies have shown that, on average, the paretic lower limb carries about 40% of the body weight,[29, 30] while it contributes to balance maintenance to a lesser extent than the non paretic limb.[29-32] This weight-bearing asymmetry does not seem to change significantly over time[28], even when motor functions recover substantially.[33]

People after stroke show an impaired performance on postural tasks necessitating proactive balance control. Anticipatory postural adjustments, essential to minimize the destabilizing effect of predictable balance perturbations, are delayed and reduced.[28] When voluntarily shifting weight from one leg to the other, they move with low speed and accuracy.[34] They show a decreased maximal weight transfer, particularly towards the paretic side.[14, 35] Self-induced arm movements result in increased body sway and delayed onsets of muscle activation patterns.[14] People after stroke therefore reduce the speed and magnitude of self induced perturbations and compensatory activate leg muscles of the non-paretic leg to regain a more stable starting position.[28]

When a postural task requires reactive balance control, people after stroke show a diminished capacity to withstand perturbations, particularly towards the paretic side.[28, 29] They show generally larger amplitudes and velocities of body sway in response to perturbations than healthy controls.[14, 28] When the perturbation intensity is small, balance can generally be restored by feet-in-place reactions (movements around the ankle or hip).[36] These reactions are delayed for people after stroke.[14, 28] Additionally, electromyographic data shows that muscle coordination patterns are disrupted, particularly of the paretic leg.[14, 37] This impaired reactive balance control after small balance perturbations is an important fall risk factor for people after stroke.[38] The risk of falling further increases with increasing perturbation intensity. A high perturbation intensity increases the speed of the traveling CoM, necessitating change-in-support strategies to adjust the BoS.[39] Indeed, stepping reactions are the ultimate strategy to prevent a fall. People after stroke show large difficulties in executing such steps[14, 28] with both the paretic and non-paretic limb.[40, 41] For instance, the initiation and start of stepping reactions are delayed, which problem increases with the intensity of the perturbation.[40] In addition, people after stroke show a reduced step length[42] and a diminished capacity to control the CoM, specifically at the end of a step (i.e. at foot landing).[41] Together, these deficits result in a diminished quality of the stepping reactions, which makes people after stroke prone to falling after a perturbation.[42, 43]

Gait

Walking is an inherently unstable activity and can be regarded as a sequence of controlled falling movements. With each step we take, the CoM travels outside the BoS in the forward direction and away from the stance leg. The next footfall of the stepping leg is critical for preventing a fall. The stepping leg thus needs to land at an optimal time and position to catch the 'falling' CoM.[44] At the same time, the stance leg is involved with providing body support and controlling the CoM movement during the act of stepping. Hence, safe walking without falling depends on both postural control and proper leg motor control, and it follows that the aforementioned postural control impairments after stroke directly impact on this capacity.

For people after supratentorial stroke, postural control and leg motor control influence gait to a large extent.[45] The unilateral spastic gait pattern as a result of this type of stroke is generally characterized by foot flat at initial contact, hyperextension of the knee at mid-stance, decreased plantar flexion at push off and/or diminished knee flexion and ankle dorsiflexion in the swing phase.[46-48] Gait impairments in the stance phase lead to instability and, consequently, to greater demands on already impaired postural control.[49] Problems in the swing phase are usually the result of impaired leg motor control and influence foot placement.[50] This leaves people after stroke at an increased risk of falling, even under steady state circumstances.

Walking in daily life also includes more demanding situations, necessitating adjustments of the ongoing steady state gait pattern to environmental constraints and demands, for instance, when maneuvering in a crowd or walking on uneven terrain. This imposes challenges to the control of the CoM.[51, 52] In addition, during adaptive gait, adequate foot placement is needed to prevent stumbling or falling[53] and impaired leg motor control becomes more evident. In general, stroke survivors perform worse on several adaptive gait tasks (e.g. turning[54], adjusting a step in the medio-lateral direction[55] and obstacle crossing[56, 57]) compared to healthy controls. During obstacle crossing, people after stroke tend to place the affected limb closer to the obstacle and show a smaller clearance of the foot.[58] In addition, CoM displacement is increased and people after stroke narrow their BoS by reducing the step length before and after the obstacle.[59] A recent study showed that for target stepping while walking, decreased speed and accuracy of stepping was associated with poorer postural control and leg motor control, respectively.[60] However, much is still unknown about the mechanisms underlying the problems with gait adaptability after stroke.

Training to prevent falls after stroke

Given the high rates of falls as a result of balance and gait deficits after stroke, one of the main goals of post-stroke rehabilitation is improving mobility and preventing falls. To achieve this goal, people after stroke often receive exercise training aimed at improving balance and gait with or without supervision of a physiotherapist.[61] In general, training after stroke should be task- and context- specific, of high intensity, and targeted towards individual goals.[10] In line with this notion, mobility outcomes (e.g. gait speed, transfers, and standing balance) improve following high intensity therapy and repetitive task training.[10, 61, 62] However, a Cochrane review on interventions to prevent falls after stroke did not show beneficial effects of exercise training on fall rates,[63] despite the fact that these interventions focused on balance and gait deficits as the key risk factors for falls. Interventions included, for instance, steady state treadmill walking, unperturbed balance and gait exercises, high intensity aerobic exercises, whole-body vibration while maintaining balance, and agility training with weight-shifting exercises. The fact that these types of interventions did not reduce fall rates or fall risk is in contrast with the overwhelming evidence of their effectiveness in the healthy elderly population.[64] The question arises whether the types of training used to prevent falls in the stroke population truly target their specific balance and gait problems. It may be that other important aspects of balance control, such as impaired trunk control and reactive stepping upon balance perturbations, are more effective targets.

The majority of training programs after stroke focus on the first months, with the highest intensity of training during inpatient rehabilitation.[10] In this period, regaining mobility is one within a wide range of goals aimed at improving activities of daily living (ADL). Training focuses on independence of steady state balance and gait. After discharge from inpatient rehabilitation, people after stroke increasingly need to face the challenging and unpredictable demands of daily living, requiring reactive balance control. These changes in the environment and postural tasks further increase the fall risk, as illustrated by an increase in fall rates immediately after discharge.[14] It therefore seems justified to introduce dynamic balance and gait training in order to prevent falls in the chronic phase after stroke.

Given the disappointing results of previous studies on exercise training to prevent falls after stroke, we first need to study which are the most important components of possibly effective training programs. To this end, we should first investigate the mechanisms underlying dynamic balance and gait problems in people after stroke and, consequently, design programs incorporating the most important components of defective balance and gait for people after stroke. Hence, 'proof-of-concept' studies are needed to evaluate whether training could actually improve these specific deficits in order to design future RCTs with falls as a primary outcome.

Outline of this thesis

This thesis addresses two main aims. The aim of **part 1** is to better understand the mechanisms underlying the problems people after stroke experience during dynamic balance and gait tasks. Thereby I focus on two important but relatively neglected components of dynamic balance and gait: trunk control and gait adaptability. In **part 2**, I aim to give insight into the effects of dynamic balance and gait training in the chronic phase after stroke and to identify which type of training could be most successful. Hereby I focus on the trainability of trunk control and stepping reactions after balance perturbations. The following research questions are addressed:

Part 1 Understanding dynamic balance and gait

1. How do people early after stroke control the relative movements of head, trunk and pelvis during lateral reaching as an example of proactive control of sitting balance.

Chapter 2 describes a kinematic analysis of a sitting lateral reach task early after stroke, focusing on the movement sequence of the head, trunk and pelvis.

2. What are the underlying mechanisms of defective gait adaptability in people after stroke?

In **chapter 3**, I describe a comparison of the motor responses of people in the chronic phase after stroke and healthy controls when performing an obstacle avoidance task.

Part 2 Training of dynamic balance and gait

3. What are the effects of exercise training on balance capacity in people in the chronic phase after stroke and which training regimen is most effective?

A systematic review and meta-analysis of randomized controlled trials evaluating the effects of exercise therapy on balance capacity in the chronic phase after stroke is described in **chapter 4**.

4. What are the feasibility and effectiveness of a stroke-specific fall prevention program in people in the chronic phase after stroke?

The development and process evaluation of the FALL prevention after Stroke (FALLS) program are addressed in **chapter 5**. In **chapter 6** a phase 1 modelling study on the effects of this program on dynamic balance and gait parameters is reported.

5. What are the effects of perturbation-based balance training on reactive step quality in people with chronic stroke?

In **chapter 7** I describe a 'proof-of-concept' study on the effects of a 5-week perturbation-based balance training program for people in the chronic phase after stroke.

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Part 1

Understanding dynamic balance and gait

Chapter 2

Kinematic analysis of head, trunk and pelvis movement when people after stroke reach sideways

Published as

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Abstract

Background. Sideways reaching in sitting is a component of a number of everyday activities and can be a challenging task early after stroke. Kinematic analysis of a lateral reach task, examining head, trunk and pelvis is needed in order to better understand motor deficits in people after stroke, and provide potential rehabilitation strategies.

Objective. The aim of the present study was to examine the difference between people with stroke and healthy controls, in movement sequence of head, trunk and pelvis, as well as the difference in angle at maximum reach and peak velocity for each body segment during reach and return.

Methods. Twenty-four people with stroke in the early phase (within 12 weeks post stroke) and 20 healthy subjects were asked to perform a standardized lateral reach. Using CODA-motion, movement sequence was determined and angles and peak velocities were calculated.

Results. When reaching, people with stroke moved their pelvis first, followed by the trunk and head, while healthy controls started with their head and then moved their trunk and pelvis. People with stroke further achieved significantly smaller angles at maximum reach when compared to healthy subjects, for all body segments. In addition, they showed lower peak velocities both during the reach (for head, trunk and pelvis) as well as the return (for head and trunk).

Conclusions. When compared to healthy controls, people early after stroke showed a different pattern of movement when performing a lateral reach. In addition, they reached less far and moved at a slower speed.

Introduction

Disability persists in over 75% of people after stroke, leading to dependency in daily activities.[1] For people after stroke to successfully execute activities of daily living, integral postural control is crucial. Early sitting balance is a well-known, independent predictor of motor and functional outcome after stroke.[2,3,4] During several activities of daily living, it is necessary to reach laterally, e.g. when grasping the salt from the other side of the table or when shuffling forward or backward while sitting on a chair. Appropriate sitting balance is key to successfully execute a lateral reach.

Throughout the literature, the biomechanical analysis of sitting balance in people after stroke has usually been examined by means of a force platform with reporting center of pressure displacements and/or velocities. Genthon et al investigated postural control during sitting in people with hemiparesis through a biomechanical analysis.[5] They showed that people with stroke had greater center-of-pressure displacements and increased velocities in comparison with healthy controls.[5] Tessem and colleagues reported that people with stroke showed more lateral displacement when reaching forward and less lateral displacement when reaching sideways to the affected side.[6] Finally, van Nes et al used a force platform to assess the recovery of quiet-sitting balance in people receiving inpatient stroke rehabilitation. They demonstrated that lateral sitting balance control was more impaired after stroke than balance in the anterioposterior direction and that lateral sitting balance showed the strongest association with the Berg Balance Scale score.[7] The authors concluded that lateral balance in a sitting position seems to be a primary target for rehabilitation.[7]

To the best of our knowledge, only a few studies addressed the kinematics of a lateral reach in people with stroke. Katz-Leurer et al found that during sideward reaching, people after stroke reached significantly less far when compared to healthy controls.[8] Campbell and colleagues investigated the speed, distance reached and angular movement of head and pelvis in a lateral reaching task in healthy subjects.[9] In addition, they assessed a small sample of people with stroke (n=5). Their subjects with stroke reached less far and with a lower speed of movement, but these differences were not significant.[9] Additional kinematic analysis on a larger sample of people after stroke as well as including the trunk together with the head and pelvis is needed in order to better understand motor deficits in people after stroke and provide potential rehabilitation strategies.

To assess differences in kinematics of a lateral reach task between people with stroke and healthy controls, a cross-sectional study was designed. The aim of this study was to examine the difference in movement sequence of head, trunk and pelvis, as well as the difference in angle at maximum reach and peak velocities during reach and return for each body segment. We hypothesized that people early after stroke would have an altered movement sequence in comparison with healthy controls, and that angles of lateral displacement and velocity of movement of head, trunk and pelvis would be decreased for people after stroke in comparison with healthy controls. Analysis of preliminary data of angular displacement of the trunk showed the lateral reach paradigm (figure 1) in which four phases were identified when performing a lateral reach: initiation, reach, return and recovery.[10,11] A detailed description of this paradigm can be found in the methods section. In an additional exploratory analysis, we examined whether this paradigm could also be applied to the head and pelvis and if there was a difference between people with stroke and healthy subjects. Duration of the phases was compared between both groups, as well as the angles and velocities during initiation and recovery. These latter phases could be of further interest when performing a lateral reach, as they might indicate preparation (initiation) or relaxation (recovery) of postural setting by means of postural adjustments prior to a reach or after a return, respectively.[12]

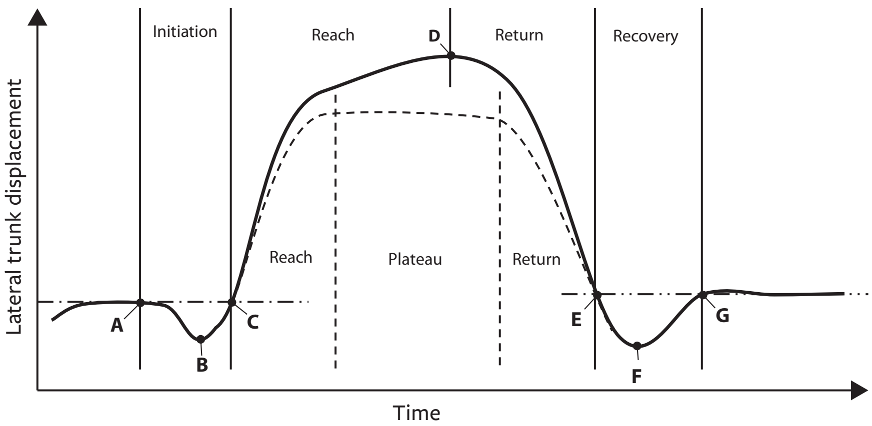

Figure 1 Lateral Reach Paradigm of the Trunk.

The paradigm based on preliminary results of angular displacement of the trunk, showing four phases of lateral reach: initiation, reach, return, recovery. Some subjects showed a plateau phase from the point of maximum reach. **A**: start of initiation **B**: peak of initiation **C**: end of initiation/start of reach **D**: maximum reach **E**: end of return/start of recovery **F**: peak of recovery **G**: end of recovery

Methods

Subjects

A total of 25 people with a first ever stroke according to the WHO definition[13] were included in this study. They had to be independently mobile prior to the stroke event. Exclusion criteria were history of other neurological impairment and other factors such as impaired vision, uncontrolled hearing, musculoskeletal and vestibular deficits or other balance disorders. They were assessed within 12 weeks after stroke. Twenty healthy adults volunteered as a control, age-matched sample. They were all aged over 60. Volunteers were excluded if there was a presence of neurological conditions, history of stroke, impaired vision, uncontrolled hearing and musculoskeletal and vestibular deficits or other balance disorders. The protocol was approved by the Isle of Wight, Portsmouth & South East Hampshire Local Research Ethics Committee. All participants provided informed consent.

Procedure

Baseline data was obtained from participants and from medical records (table 1) and included age and gender and for people with stroke the type of stroke, side of lesion, Rivermead Motor Assessment[14] and Motricity Index[15].

A lateral reach task was performed as follows (figure 2). When sitting without back and arm support, people after stroke were asked to reach with the unaffected hand to the unaffected side as far as comfortably possible. Healthy controls reached to a randomly determined side and used the same strategy and received the same command. Both groups were asked to focus on a fixed point directly in front of them to minimize any rotational component of head and shoulders. Subjects were allowed to tilt their pelvis wile reaching and to use the contralateral leg as a counter balance. Subjects were seated on a height-adjustable plinth, so that hip and knees were at 90 degrees flexion. They were asked to perform the task three times. The lateral reach task was recorded using CODAmotion (Charnwood Dynamics Ltd, UK); a 3-dimensional movement analysis system. This system is non-invasive and uses up to 24 light emitting diodes (placed on the skin) to record joint angle and time/distance factors. For our current set up, we used two markers on the face; one between the eyes and one on the chin. We also used a marker on the top of the sternum and one marker on each anterior superior iliac spine (ASIS).

Data collection

Based on preliminary results of lateral trunk movements, a paradigm was created (figure 1). This paradigm showed lateral movement of the trunk when performing a lateral reach. Before starting with the actual reach, participants showed an initiation phase in the opposite direction of the reach. Then we noted the reach phase when reaching out and the return phase when coming back to the starting position. After the return phase,

Table 1 Demographics

	People with Stroke (n=24)	Healthy Controls (n=20)
Age (mean±SE)	66±3.1	65±1.1
Gender (n (%))		
Male	19 (79)	8 (40)
Female	5 (21)	12 (60)
Type of stroke (n (%))		
Lacunar infarction	13 (54)	-
Partial anterior circulation infarction	9 (38)	-
Total anterior circulation infarction	2 (8)	-
Side of lesion (n (%))		
Right	9 (38)	-
Left	15 (62)	-
Rivermead Motor Assessment (mean±SE)		
Gross	9±0.7	-
Arm	10±1.1	-
Leg/Trunk	8±0.5	-
Motricity Index (mean±SE)		
Arm	76±5.8	-
Leg	80±3.4	-
Trunk	92±3.5	-

Participant characteristics for people with stroke and healthy subjects. The frequencies and percentages (between brackets) are given. Maximum score for the Rivermead Motor Assessment is 13 for gross, 15 for arm and 10 for leg/trunk. Maximum score for Motricity Index is 100 for each segment

(A) (B)

Figure 2 Lateral Reach Task.

Participants were instructed, from starting position (A) to reach to the side with their ipsilateral hand as far as comfortably possible (B). For people with stroke, this was done to their unaffected side; for healthy controls to a randomly determined side we observed a recovery phase with again, a trunk movement in the opposite direction of the reach. Some of our participants showed from the point of maximal reach a stable plateau, before starting with the return.

Using the CODAmotion analysis system, angles of head and trunk displacement were calculated relative to the vertical plane. We connected the two CODAmotion markers on the face to construct the vertical face reference. The vertical trunk reference was created by connecting the sternum marker with the middle of the two ASIS markers. Angles of pelvis displacement were calculated relative to the horizontal plane; the horizontal pelvis reference was constructed by connecting the two ASIS markers. Using graphs of lateral displacement of the angles, outcome measures were calculated. For each segment, first the baseline angle and time were determined (point A in figure 1). A mean was calculated for the angles of the movement before the actual reach began. If there was an initiation phase, the peak angle of the initiation (B) and time of the end of the initiation (i.e. start of reach; C) was noted. In addition, the time and angle of maximum reach (D) were determined. The start of return was defined as the point of maximum reach or as the end of the plateau (see figure 1). The final time and angle (G) were calculated similarly to those of the baseline. For files with a recovery, the peak time and angle (F) and the start of recovery (i.e. end of return; E) were noted. This was done for all subjects, for all three attempts after which a mean was calculated for each variable per subject. To calculate moving sequence of head, trunk and pelvis, we used the initial start of head movement in the lateral plane as the starting point for calculating start of the reach and return of head, trunk and pelvis.

Statistical analysis

Firstly, we visually examined the movement sequence for the reach and the return by means of plotting bar charts of start of head, trunk and pelvis movement for people after stroke and healthy controls separately. We examined whether differences between people with stroke and healthy controls as well as within-group movement sequences were significant by means of independent and paired t-tests, respectively. Secondly, angles of maximum reach for head, trunk and pelvis and peak velocity of head, trunk and pelvis during reach and return were compared between groups by means of independent t-tests. Thirdly, we calculated time of each phase as percentages and compared these normalized durations of initiation, reach, return and recovery for head, trunk and pelvis between our two groups by means of independent t-tests. Fourthly, we noted for how many people after stroke and healthy controls there was an initiation and recovery phase according to our lateral reach paradigm for head, trunk and pelvis. Finally, we examined whether there were differences in peak angle and velocity in the initiation and recovery phase between people after stroke and healthy controls by using independent t-tests. We reported mean +/- standard error for all continuous variables. All analyses were performed using SPSS Statistics (version 17.0). The alpha level was set at 0.05.

Results

For one of our 25 people after stroke, data was corrupted and had to be excluded. For all other participants, CODAmotion analysis could successfully be executed. Overall, people after stroke took longer to perform the total lateral reach task in comparison with healthy controls (12.98±0.65 sec vs. 9.88±0.71 sec, respectively; p=0.003).

Movement sequence

Figure 3 shows the movement sequence for the start of lateral reach. People with stroke relatively moved the pelvis first, followed by the trunk and head. In contrast, healthy subjects started the lateral reach with the head, followed by trunk and pelvis. Start of head and trunk movement for the reach was significantly later in people after stroke in comparison with healthy controls (head: 1.15±0.27 sec vs. 0.09±0.25 sec; p=0.07 and trunk: 0.9±0.30 sec vs. 0.14±0.12 sec; p=0.026). There were no significant differences between the body segments within both groups.

Start of movement of the different body segments for the return is shown in figure 3. No clear sequence could be observed. Start of head, trunk and pelvis movement for the return was significantly later in people after stroke in comparison with healthy controls (head: 8.89±0.67 sec vs. 5.45±0.45 sec; p<0.01, trunk: 8.28±0.60 sec vs. 5.32±0.49 sec; p<0.01 and pelvis: 8.45±0.62 sec vs. 5.48±0.45 sec; p<0.01). There were no significant differences between the body segments within both groups.

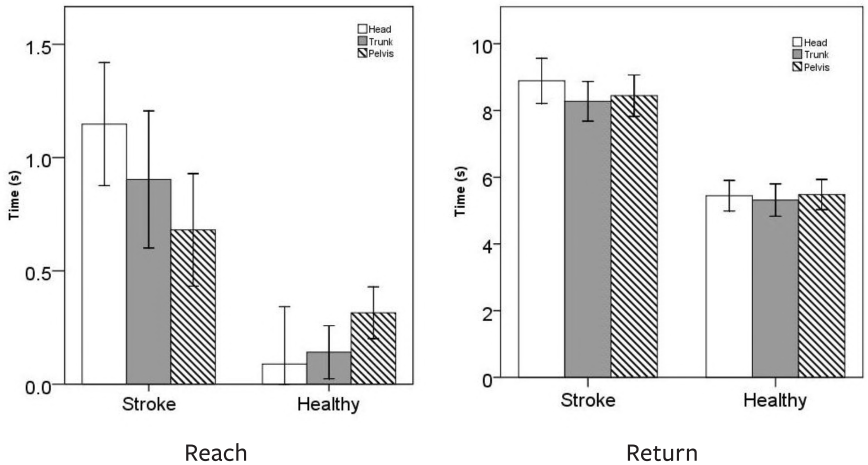

Figure 3 Movement Sequence Reach and Return.

Mean (± 1 SE) start of reach (sec) of head (white), trunk (grey) and pelvis (striped pattern) for people with stroke and healthy controls.

Reach and Return

People with stroke showed significantly smaller angles for head, trunk and pelvis position at the point of maximum reach when compared to healthy controls (table 2). Normalized durations of the reach and return phase for people with stroke was not significantly different in comparison with healthy controls, neither for head, trunk or pelvis (table 2).

Peak velocities for all body segments indicated that people after stroke were clearly slower, both when reaching and returning (table 2). This was significantly different in all body segments for the reach. For the return, this was significantly different for peak head and trunk velocity.

Table 2 Angles, normalized durations and velocities of a lateral reach

	People with Stroke mean (±SE)	Healthy Controls mean (±SE)	p-value
Maximum angle			
Head	6.61 (±2.8)	15.88 (±2.4)	0.019
Trunk	22.18 (±2.0)	38.82 (±2.2)	< 0.01
Pelvis	18.23 (±2.0)	30.06 (±1.8)	< 0.01
Normalized durations			
Head			
Initiation	8.67 (±1.85)	3.58 (±1.19)	0.035
Reach	50.03 (±2.78)	53.38 (±4.56)	0.519
Return	19.97 (±1.58)	22.71 (±1.87)	0.267
Recovery	11.18 (±1.67)	15.29 (±2.14)	0.132
Trunk			
Initiation	9.75 (±1.67)	6.99 (±1.97)	0.287
Reach	48.94 (±2.9)	46.43 (±2.25)	0.511
Return	19.95 (±1.26)	22.9 (±1.93)	0.195
Recovery	13.98 (±1.32)	22.04 (±1.13)	< 0.01
Pelvis			
Initiation	5.09 (±1.36)	3.28 (±1.19)	0.333
Reach	52.26 (±2.94)	48.72 (±2.16)	0.355
Return	22.21 (±1.8)	23.16 (±1.62)	0.701
Recovery	11.93 (±1.37)	18.2 (±1.59)	< 0.01
Peak Velocities			
Reach			
Head	12.94 (±1.5)	19.25 (±9.1)	0.016
Trunk	14.80 (±2.0)	30.05 (±2.5)	< 0.01
Pelvis	12.65 (±1.6)	25.90 (±3.0)	< 0.01
Return			
Head	14.83 (±1.5)	27.47 (±2.4)	< 0.01
Trunk	19.53 (±2.1)	32.14 (±2.7)	< 0.01
Pelvis	20.22 (±2.2)	27.27 (±3.5)	0.083

Maximum angles (degrees), normalized durations (%) and peak velocities (degrees/sec) for all body segments, and with corresponding p-values.

Initiation and recovery

For the head, an initiation was seen in 50% of people after stroke and 25% of healthy controls, a recovery was seen in 75% and 85%, respectively. More initiations were observed in the trunk; 67% in people after stroke and 80% in healthy controls. This was also the case for recovery of the trunk; 92% and 95%, respectively. Fewer initiations were noted for pelvis movement in people after stroke (46%) and healthy controls (35%), whereas the incidence of recovery was similar to that one of the trunk (92% and 95% for people after stroke and healthy controls, respectively).

In people after stroke, there was a significantly longer duration of the initiation of head movement in comparison with healthy controls (table 2). For people with stroke, we also found a shorter recovery for trunk and pelvis movement compared to healthy controls (table 2).

For those participants who showed an initiation or recovery, no differences in peak angle of head, trunk and pelvis position were seen between both groups. We only noted smaller peak velocities in people after stroke for the second part of trunk initiation (6.27±0.92 deg/s vs. 12.09±1.58 deg/s; p=0.002) and the first part of trunk recovery (13.75±1.22 deg/s vs. 21.06±1.91 deg/s; p=0.003) in comparison with healthy controls.

Discussion

The aim of this study was to conduct a kinematic analysis of the lateral reach; a frequently used clinical task in stroke rehabilitation, where participants are in a sitting position and reach to the side as far as comfortably possible and subsequently, return to the starting position. We were interested in the sequence of movement as well as the lateral displacement and velocity of head, trunk and pelvis during a lateral reach and we hypothesized that people after stroke would have an altered sequence of movement and that our kinematic parameters would be decreased in people after stroke in comparison to healthy controls.

Our results with regard to movement sequence at the onset of reach did show an altered pattern of movement. People after stroke had a relatively contrary movement sequence in comparison with healthy controls with significantly longer onset latencies of head and trunk movement in the lateral plane. We observed a relative top-to-bottom movement sequence in healthy controls; the head moved before the trunk and the trunk before the pelvis. This might be as one expects and is in line with the top-to-bottom movement sequence presented in literature examining whole-body coordination while turning in healthy controls.[16] Our relatively contrary results for people early after stroke indicated that the pelvis moved first followed by the trunk and head. In our study, movement was defined as a deviation from the horizontal room axis in the case of the pelvis and from the vertical room axis in the case of trunk and head. This means that our sample of people after stroke started to move from the pelvis but they kept trunk and head aligned in their original position when reaching sideways, which suggests an 'en bloc' movement. The point where the trunk and head then started to move away from the vertical room axis was found to be significantly delayed when compared to healthy controls. Reisman & Scholz examined surface force production during lateral seated reaching and found a delayed onset of medio-lateral seat force which seems to be in line with our present findings.[17]

Our results for the movement sequence of the return showed very similar patterns for both groups, but people after stroke started to move their head, trunk and pelvis significantly later than healthy controls. It is important to be cautious when interpreting these results, because the onset of the movement of the body segments for the return are relative to the initial lateral head movement of the reach. Nevertheless, it is noteworthy that for healthy controls and people after stroke, the movement sequence was very comparable and in this prospect different from the result from the reach. This difference could be explained in several ways. When reaching sideways, away from the base of support, muscles have to work concentrically and the person is moving to a more unstable position. On the return, muscles have to work eccentrically and control the descent towards the starting position, thus one is moving towards a safer position. It might be the case that the assistance of gravity in the return phase of the lateral reach is a less challenging task and facilitates a movement pattern more closely related to that seen in healthy controls. To the best of our knowledge, this movement sequence has not been described in the literature before and is of interest for clinical practice. The fact that onset latencies for head, trunk and pelvis movement in the return phase were delayed in people with stroke in comparison with healthy controls can be explained by the result of a post-hoc analysis using the raw times, indicating that the time it took to achieve the point of maximum reach was significantly longer for people after stroke in comparison with healthy controls. However, this difference was not significant in the normalized times that we presented here (table 2). We decided to present normalized times based on the fact that overall times for the lateral reach were significantly different between both groups. Furthermore, one should note that not only peak velocities were significantly decreased for people after stroke but also maximum angles. These two variables combined could also explain the discrepancy found between significant delay of onset latency for the return and non-significant normalized durations of the reach and return phase.

At the point of maximum reach, angles of the head, trunk and pelvis were significantly lower for people after stroke in comparison with healthy controls, which confirms the findings of other researchers.[6-9] Our study contributes to the body of knowledge of kinematics of the lateral reach in people after stroke and more specifically, we were able to confirm the findings of Campbell et al who suggested that people after stroke reached less far and had lower speed of movement when reaching to the side.[9] Their study included a limited sample of people after stroke (n=5) and they only observed head and pelvis movement. In our study, we were able to recruit a larger number of participants and included head, trunk and pelvis measurements during the reach as well as the return. We found significant differences for peak velocity for all segments during the reach and for the head and trunk during the return. Further studies could investigate how these findings progress during the recovery from the very early stage after stroke until the chronic phase, as well as the relation with motor and functional outcome after stroke. Further research into this area seems justified based on our results as well as from previous literature looking into the clinical measurement of a lateral reach.

There are standardized clinical tests or scales assessing lateral trunk control in the literature. A simple functional reach test is commonly cited in the literature and Katz-Leurer and colleagues recently re-examined its reliability and validity.[8] They found high reliability of their modified lateral functional reach test (ICC > 0.90) as well as a moderate, significant correlation between their test and Balance Master measures, indicating validity of a simple functional reach. In addition, the dynamic sitting balance subscale of the Trunk Impairment Scale[18,19] examines lateral trunk control and in a pilot randomized controlled trial, it was reported that a five-week intervention significantly improved lateral trunk control in favor of the control group. It was suggested that trunk exercises aimed at improving sitting balance and selective trunk movements have a beneficial effect on the selective performance of lateral flexion of the trunk after stroke.[20]

We examined in more depth our original paradigm of lateral trunk movement (figure 1) during the lateral reach with four phases: initiation, reach, return and recovery. We proposed that this paradigm could also be applied to lateral movements of the head and pelvis and by utilising the four phases, to describe angles and velocities throughout the movement cycle. The recovery phase at the end of the return was of particular interest in our study. Some of our participants demonstrated an adjustment of body position following an overshoot. We believe this relates to the fact that peak velocities for the return were relatively higher than for the reach; for all segments and for both groups. Bringing a body segment back to its starting position and controlling the eccentric descent apparently involves obtaining control over an overshoot of this body segment after the return phase. We also noted a significantly shorter duration of recovery for trunk and pelvis in people after stroke. We believe this could relate to the fact that people after stroke reached significantly less far than healthy controls and therefore, less eccentric trunk and pelvis movement was needed. We believe this also explains the smaller peak trunk velocity found in the first part of trunk recovery.

Limitations and directions for future research

Although larger than most studies in this field, our sample was relatively small and only mildly impaired. Therefore, we believe the study should be replicated on a group of very acute people with stroke with more severe impairments. Furthermore, we evaluated the lateral reach only in one direction: to the unaffected side for people after stroke. This was based on (1) the fact that our task was part of a larger protocol which included different clinical tasks as well as 3-D observations and (2) people after stroke in our study generally had an upper limb impairment and could not bring their arm in the standardized position to perform a lateral reach task. In addition, we focused on lateral displacements in our analysis and acknowledge that there might be a rotational component as well as a displacement in the sagittal plane when reaching to the side. By asking our subjects to focus on a visual target in front, we believe we have minimized these additional movements in order to obtain optimal standardization of our clinically important task. Finally, further suggestions for future studies could include the use of three markers to determine the center of the pelvis; the kinematic analysis of the upper (shoulders) and lower part of the trunk (pelvis) separately, and the inclusion of a biomechanical analysis of the supporting role of thighs and feet.

Conclusion

Our cross-sectional study of the kinematic analysis of the lateral reach in people after stroke showed clear deficits of head, trunk and pelvis movement in the different phases of the lateral reach. Reduced peak angles and velocities of head, trunk and pelvis movement indicated that people after stroke with mild motor impairments have kinematic impairments when performing a lateral reach. These findings can inform clinical practice as a lateral reach is a common activity in rehabilitation and everyday life. Therapists and people with stroke should be alerted to the reduced movement and the tendency to move en bloc which suggests less freedom to move or to respond to disturbances of stability. It could be argued that the emphasis in rehabilitation should be on providing opportunities to facilitate total body movement and movement at the different sections of the body during functional tasks such as reaching. Speed of movement should be monitored and trained, with emphasis on the control of eccentric descent during lateral reach.

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Chapter 3

Deficits in motor response to avoid sudden obstacles during gait in functional walkers post stroke

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Abstract

Background. Safe community ambulation requires the capacity to adapt gait to environmental changes on short notice. A reduced gait adaptability may contribute to an increased fall risk.

Objective. This study investigated gait adaptability in community-dwelling persons post stroke and sought to understand some of the mechanisms underlying the expected loss of gait adaptability.

Methods. Participants were 25 post-stroke persons (Functional Ambulation Categories score 5) and 25 healthy controls of similar age. During treadmill walking, 30 obstacles were suddenly dropped in front of the affected (post-stroke persons) or left (controls) leg. The participants had to avoid the obstacle by either lengthening or shortening the ongoing stride. The obstacle avoidance success rates were determined. Furthermore, the electromyographic (EMG) activity of bilateral biceps femoris, rectus femoris, tibialis anterior and gastrocnemius medialis muscles were recorded as well as concomitant knee and hip angle courses and spatial characteristics of the avoiding stride.

Results. Post-stroke persons demonstrated markedly decreased obstacle avoidance success rates, most prominently under time pressure. Furthermore, they showed delayed and reduced EMG responses, smaller joint angle deviations from unperturbed walking, and smaller horizontal margins from the foot to the obstacle.

Conclusions. Even in persons who were only mildly affected by stroke, gait adaptability seems to be reduced, which may place them at risk of falling. Delayed and decreased muscle responses were identified as one of the possible mechanisms underlying this reduced capacity. The consequent kinematics explained why participants with stroke were less able to adequately adapt the length of the avoiding stride.

Introduction

People in the chronic phase of stroke are at an increased risk of falling compared to healthy age-matched peers.[1] This high risk is evident even among well-recovered community-dwelling individuals.[2] For independent and safe community ambulation, it is particularly important to be capable of adapting the gait pattern to environmental demands and constraints, as confirmed by reports of an increased fall risk in people with reduced gait adaptability.[3]

It has been shown that gait adaptability is reduced in people with stroke[4-6]. People with stroke demonstrated deficits in visually[4] or auditory[5, 7] evoked online step adjustment. In good walkers, current clinical tests usually fail to demonstrate these more subtle gait impairments. Hence, gait adaptability tests that challenge people at the limits of their capacity may uncover problems that otherwise remain unnoticed in common observational clinical evaluation.

Although there is strong evidence that gait adaptability is compromised after stroke, the underlying mechanisms are still largely unknown. Deficits in movement execution were demonstrated when people with stroke had to approach and cross an obstacle that was positioned several strides ahead.[8] However, deficits in step adaptations became even more prominent when they had to be executed under time pressure.[4, 9] Therefore, a delay in the commencement of the adaptation most likely further reduces their gait adaptability. Indeed, in healthy older individuals, both decreased response amplitudes and delayed reaction times have been associated with reduced gait adaptability.[10]

It is important to elucidate the mechanisms underlying reduced gait adaptability after stroke, because this knowledge adds to our understanding of the problems that these people experience while walking in the community and may provide targets for intervention. Hence, in the current study, we aimed to study gait adaptability in community-dwelling people with stroke. In particular, we aimed to address some of the mechanisms underlying the expected decrease in gait adaptability. A time-constrained obstacle avoidance paradigm on the treadmill has often been used to evaluate gait adaptability[3, 4, 11-14] and may predict falls in daily life.[3] Moreover, treadmill walking is considered a valid method for detecting motor control deficits post stroke.[15] Therefore, the present study compared the ability to avoid sudden obstacles during treadmill walking between post-stroke persons and healthy control subjects. We used electromyography (EMG) to investigate muscle response times and amplitudes and we explored the relationship of EMG with kinematic and spatial characteristics of the avoidance maneuver.

Methods

Participants

The experimental group consisted of 25 persons with hemiparesis at least 6 months post stroke. The data of this group were collected as part of a study comparing functional electrical stimulation (FES) of the peroneal nerve with an ankle-foot orthosis (AFO),[16, 17] so all participants demonstrated stroke-related foot drop during gait. In addition, candidates had to be able to walk independently without a walking aid for more than 10 minutes on even and uneven surfaces (Functional Ambulation Categories score 5[18]) and to walk comfortably on the treadmill without handrail support at 2 km/h or faster. Exclusion criteria that were relevant for the current study were visual impairments and an impaired understanding of instructions. Other FES-related exclusion criteria were a demand-type pacemaker, pregnancy, psychological disorders (depression or psychosis) and, related to the paretic limb, less than 30 degrees of passive ankle motion, inability to load the heel while standing upright, severe hypertonia of the calf (Modified Ashworth Scale scores 4-5[19]), skin lesions at the electrode sites and inability to stimulate the peroneal nerve. The following clinical measures were obtained: muscle tone of the knee and ankle muscles (Modified Ashworth Scale[19]), lower extremity muscle strength (Motricity Index[20]), lower extremity motor selectivity (Fugl-Meyer Assessment[21]), balance (Berg Balance Scale[22]), and comfortable walking speed. For the control group, we recruited 25 healthy participants of similar age. All participants gave written informed consent. The experimental protocol was approved by the regional medical-ethical committee.

Experimental setup

The participants with stroke walked on a treadmill with their AFO at either 2 or 3 km/h, depending on their individual walking capacity (Figure 1a). The controls walked at both 2 and 3 km/h. We post-hoc 'matched' controls to the persons with stroke and only analyzed the series performed at the same speed. All participants wore comfortable shoes and a safety harness that did not support any body weight. Just above the treadmill, an obstacle (length, width and height: 40, 30 and 1.5 cm, respectively) was held by an electromagnet.[23,24] The participants were instructed to maintain a sagittal distance of about 10 cm between the hanging obstacle and the avoiding foot at the moment of foot strike (Figure 1a).

Three reflective markers were attached at the most anterior, posterior and lateral part of each shoe, and one additional marker was placed at the front edge of the obstacle. A 6-camera 3D motion analysis system (Vicon Motion Systems[a]) recorded the marker positions at 100 Hz. Foot marker data were processed in real time to determine the instant and position of foot strike. Computer algorithms used this information to trigger obstacle release unexpectedly (after 5-15 unperturbed strides) in one of three phases of the gait cycle: mid-stance, stance-swing transition, and mid-swing. Later instants of obstacle release reduced the time available to respond to the obstacle and, consequently,

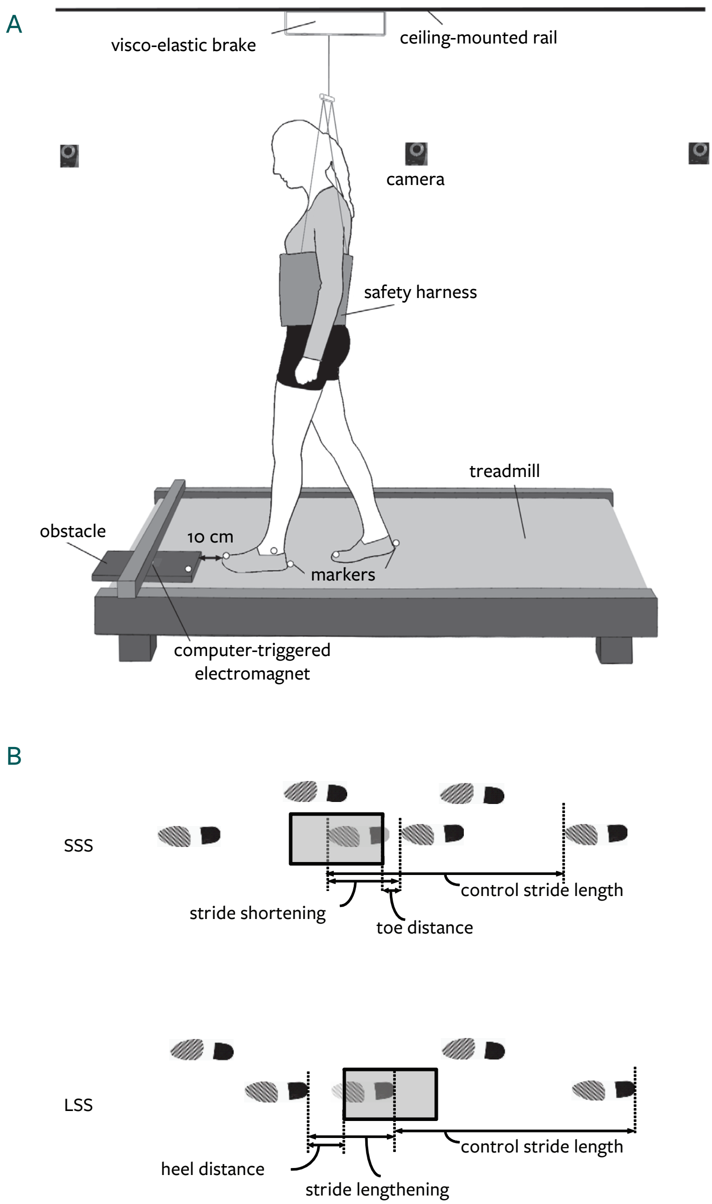

Figure 1 (A) Schematic diagram of the experimental setup. (B) Schematic diagram of the avoidance strategies: Short Stride Strategy (SSS): an additional shortened stride is performed before the actual crossing stride. Long Stride Strategy (LSS): the stride is lengthened to cross the obstacle.

increased the level of difficulty of the trial. The three phases of obstacle release corresponded with available response times (ART) of 450-600, 300-450 and 150-300 ms, respectively. ART was defined as the time span between obstacle release and the moment that the toe would have crossed the front edge of the obstacle in case of an unaltered walking pattern.

The obstacle always fell in front of the affected leg of the post-stroke persons and the left leg of the controls, which will be referred to as the 'avoiding leg'. Participants were instructed to avoid stepping on the obstacle, while stepping aside with the avoiding leg was not allowed. The other leg, called the 'stance leg', was not obstructed by the obstacle. Contact of the foot with the obstacle and steps beside the obstacle with the avoiding leg were classified as failures, which was judged by two assessors. In the case of any uncertainty, we checked the marker position data and video recordings of the respective trial to underscore a final decision. At the beginning of each session, the participants got time to familiarize with treadmill walking and, in addition, they performed 5 practice obstacle avoidance trials. Subsequently, they performed 30 experimental obstacle avoidance trials in which the instants of obstacle release (mid-stance, stance-swing transition and mid-swing) were randomly distributed over the trials. Total walking time was approximately 20 minutes and breaks were permitted whenever needed.

Electromyographic (EMG) recordings were made of bilateral biceps femoris (BF), rectus femoris (RF), tibialis anterior (TA) and medial head of gastrocnemius (GM) muscles. We used self-adhesive electrodes (Tyco Arbo ECG[b]) that were attached according to SENIAM guidelines.[25] Furthermore, flexion-extension movements of the hips and knees were measured with goniometers (Biometrics SG150 and SG110/A[c]). EMG and goniometer signals were recorded synchronously with the marker data at a sample rate of 1000 Hz.

Data processing

Individual avoidance success rates were calculated for each of the ART categories. From the marker data it was determined for each trial whether the subject had avoided the obstacle by shortening (short stride strategy; SSS) or by lengthening (long stride strategy; LSS) the ongoing stride (Figure 1b). The LSS is generally used at long ARTs, whereas the SSS is used at short ARTs.[26, 27] In 5.1% of the trials, a strategy was applied that could not be classified as either SSS or LSS. These trials were discarded from the analysis. For each ART category, the proportions of LSS and SSS trials were computed.

Spatial outcomes included the distance from the toe to the obstacle (toe distance) for SSS trials, from the obstacle to the heel (heel distance) for LSS trials, and the amount of stride shortening (SSS) or lengthening (LSS), defined as the deviation from the mean control stride length (i.e. length of the stride prior to obstacle release for each trial; averaged over all 30 trials).

Goniometer data were low pass filtered (6 Hz; zero lag, fourth order Butterworth). Subsequently, we determined the maximum hip and knee flexion angles during the swing phase of the avoiding leg, and the maximum knee flexion and hip extension angles during the stance phase of the stance leg. Outcomes were computed for each trial as the deviation from the mean control stride (i.e. averaged over 30 trials) and were averaged within each subject over all SSS and LSS trials.

The EMG signals were band-pass filtered (20-450 Hz; zero lag, fourth order Butterworth), full-wave rectified and low-pass filtered (25 Hz; zero lag, fourth order Butterworth). For each muscle and each participant we calculated the average (±2SD) trajectory over the 30 control strides. Muscle onsets were detected by a computer algorithm with visual inspection as a control. Onset was defined as the moment at which the EMG activity of the perturbed step exceeded the mean plus 2 SDs of the control strides at the respective instant of the step cycle for at least 30 ms (figure 2). Onset latency was the time between obstacle release and muscle onset. We calculated the EMG amplitudes over the initial 100 ms following response onset (figure 2, arrow *a*), because we expected that this time period would be essential to successful performance due to the time-critical nature of the avoidance task. In addition, we calculated the 'late' response amplitudes from 100 ms after response onset until foot strike (figure 2, arrow *b*). For both initial and late muscle response amplitudes, the extra amplitude (i.e. additional to the average control stride) was normalized to the mean control amplitude of the corresponding phase of the stride.

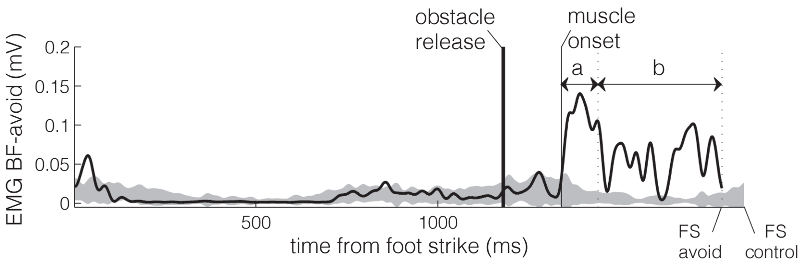

Figure 2 Example of electromyography (EMG) onset detection in a control subject.

The solid trace represents an example of left biceps femoris response (BF-avoid) to obstacle release (from foot strike to foot strike of the avoiding stride). This BF-avoid trace is superimposed on a grey area representing the EMG activity of this muscle during unperturbed gait (ie,. mean ± 2 SD of control strides).The thin vertical solid line gives the start of BF-avoid deviation from this area (muscle onset). Muscle onset latency is the time difference between muscle onset and obstacle release. Arrow *a* indicates the 100-ms-period over which the ''initial'' response amplitude was computed. Arrow *b* indicates the period of the avoiding stride over which the 'late' response amplitude was computed. FS = foot strike; FS avoid = foot strike of the avoiding stride; FS control = foot strike of the control stride.

Statistical analysis

First, success rates and the proportions of LSS and SSS were compared between the groups by means of a 2-way ANOVA with *ART* (150-300, 300-450, 450-600) as a within- and *Group* as a between-subjects factor. All trials, irrespective of successfulness, were further analyzed. Spatial outcomes were compared between the groups with Student *t*-tests. Further, we subjected each of the kinematic outcomes to a 2-way ANOVA (*Strategy* by *Group*).

EMG onset latencies and initial response amplitudes were subjected to a 2-way ANOVA with *Muscle* (8 levels) as a within- and *Group* as a between-subjects factor. In this analysis, the results were collapsed over both avoidance strategies, because the activation sequence was not different between LSS and SSS (*Strategy* × *Muscle* on onset latencies, $p=0.275$), nor were there any differential effects of strategy between the groups (*Strategy* × *Group* × *Muscle*, $p \geq 0.302$). In contrast, late response amplitudes were compared between the groups by means of 2-way ANOVAs for SSS and LSS trials, separately. The significance level in these analyses was adjusted to 0.025% to correct for multiple testing.

Post-hoc analyses were performed using Student *t*-tests with Bonferroni correction for multiple comparisons. For all primary tests, the (uncorrected) alpha level was set at 0.05.

Results

Participants

Table 1 summarizes the characteristics of the participants. The groups did not differ in age, gender, weight or body height. All but one participant with stroke wore an ankle-foot orthosis (AFO) to correct drop foot. In one participant, a trip occurred during one of the assessments. This single obstacle avoidance trial was excluded from the analysis.

Obstacle avoidance success rates and avoidance strategy

The controls hardly ever touched the obstacle (average success rate 96.9±1.0%), whereas the people with stroke were successful in merely 30.3±4.7% of the trials (*Group* main effect, $F(1,48)=192.02$, $p<0.001$, $\eta_p^2=0.80$; figure 3). The difference in success rates increased with increasing time pressure (*Group*×*ART*, ($F(2,96)=15.38$, $p<0.001$, $\eta_p^2=0.243$).

The strategy used to avoid the obstacle was not different between the participants with stroke and controls (*Group* main and interaction effects, $F<1.98$, $p>0.143$), and ART was not different between the groups, neither for LSS ($t(42)=0.76$; $p=0.452$) nor for SSS ($t(46)=1.08$; $p=0.285$). The strategy used depended on ART, with the SSS being more prevalent at shorter ART ($F(2,96)=88.53$, $p<0.001$, $\eta_p^2=0.65$; figure 2).

Table 1 Characteristics of the participants.

	Stroke (n=25)	Control (n=25)
Mean age, years (range)	51 (21-68)	51 (23-72)
Sex, male/female, n	20 / 5	18 / 7
Mean body weight, kg (range)	82.6 (53-131)	73.8 (49-98)
Mean body height, m (range)	1.76 (1.53-1.89)	175 (1.60-1.90)
Mean time post stroke, months (range)	41.4 (7-105)	NA
Hemisphere of stroke, left/right, n	15 / 10	NA
Type of stroke, infarction/haemorrhage, n	19 / 6	NA
Median Modified Ashworth Score (0-5)[a] (range)		
Knee flexors / extensors	0 (0-4) / 0 (0-2)	NA
Ankle plantar / dorsal flexors	0 (0-3) / 0 (0-1)	NA
Median lower-extremity Motricity Index (0-100)[a] (range)	64 (27-83)	NA
Median lower-extremity FMA (%) (range)[a]	68 (21-93)	NA
Median Berg Balance Scale (0-56) (range)	53 (41-56)	NA
Mean comfortable walking speed, m/s (range)	1.07 (0.67-1.67)	1.35 (1.03-1.60)

Abbreviations: FMA = Fugl Meyer Assessment (% of full recovery); NA= not applicable.
[a] Scores of the paretic body side.

Spatial characteristics

In table 2, spatial characteristics of the avoidance maneuver are shown. In SSS, participants with stroke decreased their pre-crossing stride length to a lesser extent than controls ($t(46)=7.228$, $p<0.001$). Consequently, in successful trials their toe distances were significantly shorter ($t(36)=2.710$, $p=0.010$). In LSS, they demonstrated less stride lengthening ($t(42)=5.463$, $p<0.001$), and heel distances in successful trials tended to be smaller compared to the control subjects ($t(39)=1.864$, $p=0.07$). Averaged over all trials, the participants with stroke showed negative values for both heel and toe distances, indicating that the foot landed on the obstacle in the majority of the trials.

Kinematics

Bilateral joint angle courses of the hips and knees are shown in figure 4. In SSS, the knee of the avoiding leg landed in a more flexed position at foot strike compared to unperturbed walking. This phenomenon was more prominent in the controls (+28.2±1.5°) than in the stroke group (+4.5±1.2°, $p<0.001$). Furthermore, maximum hip flexion became less, again more prominently in the controls (-4.2±0.5°) than in the stroke group (-0.3±0.8°, $p<0.001$). As for the stance leg, the hip was less extended in late stance compared to unperturbed walking. The 7.0±0.5° decrease in hip extension angles in the controls was larger than in the participants with stroke (4.1±0.8°, $p=0.004$).

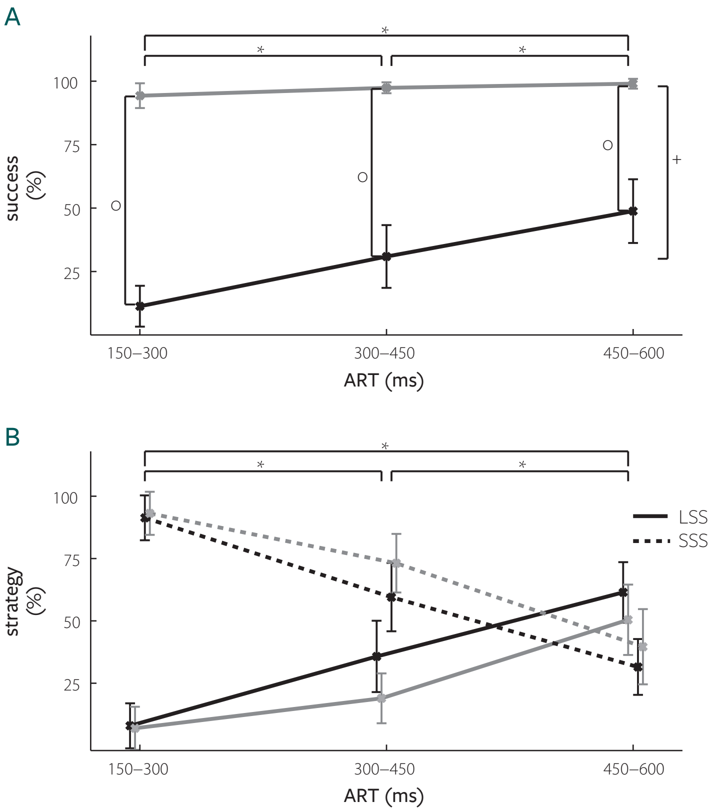

Figure 3 (**a**) Obstacle avoidance success rates (mean [CI]) for each of the available response time (ART) categories. (**b**) Rates of obstacle avoidance strategy (mean [CI]), for each of the groups and ART-categories.

All outcomes for the stroke group are shown in black and for the controls in grey. The long stride strategy (LSS) is shown in solid lines and the short stride strategy (SSS) in dotted lines. Significant main effects are indicated for *Group* (plus-sign) and *ART* (asterisks). In case of a significant *Group* by *ART* interaction, significant post-hoc effects between the groups are indicated with a circle.

In LSS, knee flexion angles during the swing phase increased in the avoiding leg compared to unperturbed walking, which tended to be more pronounced in the controls (+12.6±10.7°) than in stroke group (+4.8±2.2°, p=0.036). In the stance leg, the knee was more flexed during the stance phase, which was more pronounced in the controls (+8.6±1.8°) than in the participants with stroke (+3.7±1.0°, p=0.018).

Table 2 Spatial characteristics of the obstacle avoidance parameters[a].

	Stroke	Control
Control stride length (m)	0.81 (0.12)	0.90 (0.11)*
Stride shortening in SSS (m)	0.11 (0.10)	0.30 (0.08)**
Stride lengthening in LSS (m)	0.29 (0.10)	0.44 (0.09)**
SSS toe distance of successful trials (m)	0.09 (0.06)	0.15 (0.07)*
SSS toe distance of all trials (m)	-0.06 (0.08)	0.14 (0.07)**
LSS heel distance of successful trials (m)	0.04 (0.03)	0.07 (0.06)
LSS heel distance of all trials (m)	-0.09 (0.10)	0.07 (0.07)**

Abbreviations: SSS: short stride strategy; LSS: long stride strategy;
[a]Values are mean ± standard deviation
the asterisks indicate significant differences between the groups (**p* < .05,***p* < .001).

EMG muscle responses

In the healthy controls, the first response to the obstacle was consistently observed in BF-avoid and RF-stance (figure 5b). These muscles also demonstrated the highest rates of occurrence (figure 5a) and the largest response amplitudes (figure 5c). Responses in the other muscles followed after ~30-80 ms in a variable sequence.

In persons with stroke, the number of trials in which an EMG onset could be detected was generally lower and the activation sequence was less consistent than in controls. The onsets of particularly BF-avoid, RF-stance and GM-avoid were delayed in the stroke group compared to the controls by 41, 39 and 36 ms, respectively, without significant delays in the other muscles (BF-avoid (mean±SD) 194±32 vs. 154±19 ms; RF-stance 206±26 vs. 167±21 ms; GM-avoid 226±43 vs.191±29 ms for stroke and control group, respectively; *Group* × *Muscle*, $F(5.46,256.77)=4.99$, $p<.001$, $\eta_p^2=.096$).

The initial response amplitudes (in the first 100 ms from onset; figure 5c) were lower for persons with stroke, particularly in BF-avoid (328±143% vs. 1754±1042% for stroke and control group, respectively) and RF-stance (226±197% vs. 1115±871%). Significantly lower amplitudes were also observed in GM-avoid (361±274% vs. 994±826%) and BF-stance (309±182% vs. 755±482%; *Group* × *Muscle*, $F(3.44,161.67)=17.86$, $p<.001$, $\eta_p^2=.275$).

Late response amplitudes were analyzed for SSS and LSS, separately. In SSS (figure 5*d*), most muscles demonstrating lower initial response amplitudes in the stroke group also showed significantly lower late response amplitudes (i.e. BF-avoid, RF-stance and BF-stance; *Group* × *Muscle*, $F(2.01,80.34)=5.55$, $p=0.005$, $\eta_p^2=.122$). In contrast, late response amplitudes in TA-avoid tended to be larger in the stroke group (with 390±460%) than in the controls (156±160%; $p=0.007$).

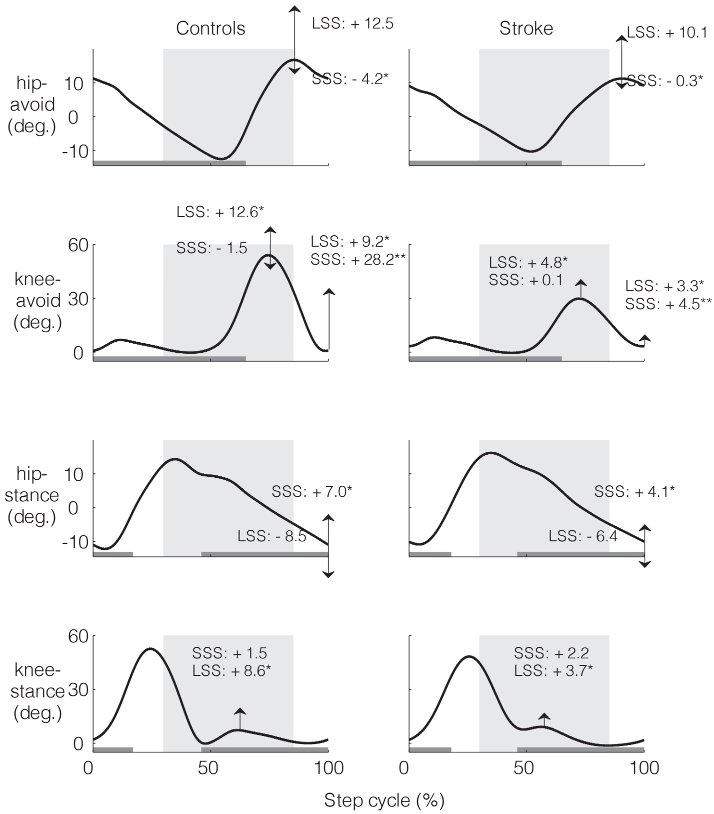

Figure 4 Bilateral joint angle courses (hip, knee) from foot strike to foot strike of the avoiding leg during control strides.

The mean individual trajectories were averaged over the healthy controls (left) and stroke group (right). Arrows indicate the mean increase or decrease in maximum joint angles (°) during short stride strategy (SSS) and long stride strategy (LSS) compared with the control stride. Increases or decreases that differed significantly between the groups are indicated with an asterisk. Grey horizontal bars indicate the stance phase of the leg. The time span within which an obstacle may be dropped is depicted as a shaded area for each of the windows. The extension ''-avoid" to the joints indicates the leg in front of which an obstacle was dropped, which was the affected leg for the stroke group and the left leg for the controls. The other leg is indicated with the extension ''-stance".

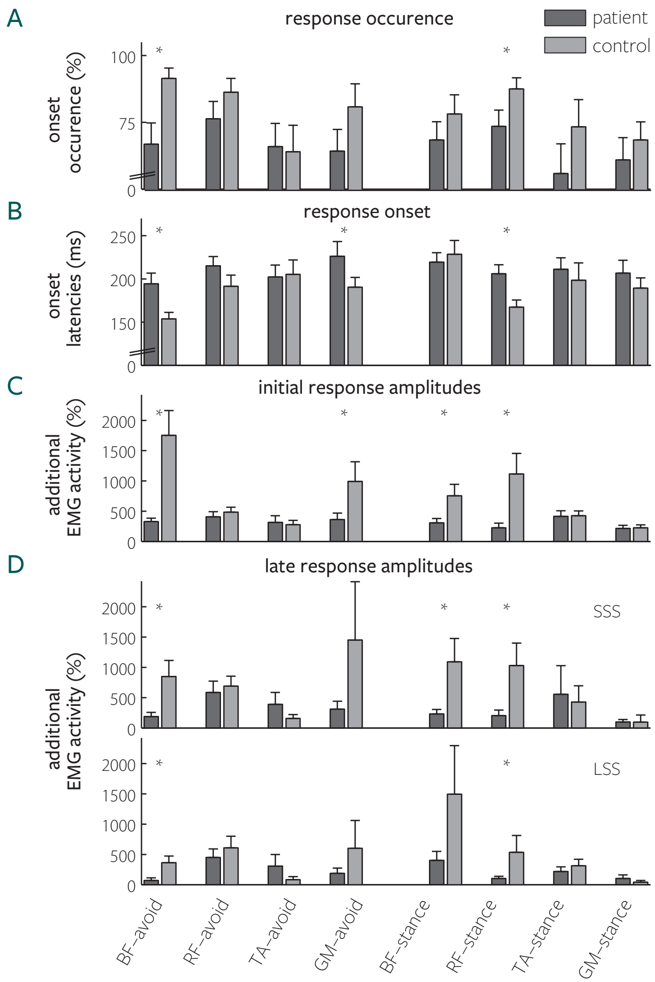

Figure 5 Electromyography (EMG) muscle responses to the obstacle (mean + CI).

(**A**) Percentage of trials in which an EMG onset could be detected. (**B**) Onset latencies, the time span between the moment of obstacle release and start of EMG deviation from control stride during unperturbed gait. (**C**) Response amplitudes computed over a time span of 100 ms following EMG onset. (**D** and **E**) Response amplitudes computed between EMG onset and subsequent foot strike for short stride strategy (SSS; D) and long stride strategy (LSS; D). Response amplitudes were normalized with respect to the average (over 30 strides) amplitude in the corresponding phase of the step cycle during unperturbed gait. Values represent the amount of additional EMG activity compared with unperturbed gait. *BF*, biceps femoris, *RF*, rectus femoris, *TA*, tibialis anterior, *GM*, medial head of gastrocnemius. "Avoid": muscle of the avoiding leg; "Stance": muscle of the stance leg. The Bonferroni corrected level of significance in post-hoc t-tests was .006 (A-C) and .003 (D and E). Significant differences between the groups are indicated with asterisks.

Late response amplitudes in LSS (figure 5*d*) were also lower for BF-avoid and RF-stance in the participants with stroke compared to the controls (BF-avoid 71±103% vs. 363±261%; RF-stance 104±83% vs. 535±648%, respectively; *Group* × *Muscle*, $F(1.97,66.8)= 6.81$, $p=0.002$, $\eta_p^2=.167$). In contrast and similar to the results for late response amplitudes in SSS, the stroke group demonstrated larger TA-avoid amplitudes (308±456%) compared to controls (84±104%; $p=0.012$). This effect, however, was not significant due to the corrected alpha level.

Discussion

The present study demonstrated that post-stroke people had major difficulties avoiding obstacles while walking, particularly when there was little time to execute the stride adjustment. This reduced gait adaptability confirms earlier reports of obstacle avoidance problems in people with stroke.[4] In addition, this study identified some of the underlying motor impairments that explain the frequently observed obstacle contacts. People with stroke demonstrated delayed and reduced EMG responses, smaller changes in hip and knee joint angles (compared to unperturbed walking) and smaller horizontal margins of the foot to the obstacle. In contrast to the study of Den Otter and co-workers[4], we found no between-group differences concerning the avoidance strategies used. Hence, the decreased success rates in the participants with stroke were probably not related to the application of inappropriate avoidance strategies.

The SSS was predominantly applied in the most difficult trials (i.e. with short ARTs; figure 3b). The stride shortening was achieved by a quick deceleration of the forward swing of the avoiding leg such that the hip was flexed less and the knee at foot contact was flexed more than in normal gait. However, in the people with stroke, these changes in joint angles were less pronounced than in the controls. This was most likely due to their BF-avoid delayed onsets and decreased activation levels (both initial and late response amplitudes). As a result, they often failed to sufficiently shorten their stride and landed on the obstacle with the toes (table 2). With respect to the lower-leg muscles, the controls presumably activated their GM-avoid early and at high amplitudes in preparation for weight bearing on the forefoot, as the stride shortening (with considerable knee flexion) often resulted in a forefoot landing at initial contact. In contrast, the people with stroke landed on the obstacle with their toes in most SSS-trials, with the knee almost as extended as in the control strides. The use of an AFO may have prevented them from using a strategy with ankle plantar flexion and knee flexion. These participants may have attempted to avoid the obstacle by activating TA-avoid to hold the forefoot above the obstacle, while keeping the heel on the treadmill surface. In this perspective, the larger TA-avoid amplitudes in the stroke group may be regarded as a compensatory strategy for the delayed and decreased activity of BF-avoid. Nevertheless, this compensation was unsuccessful in the vast majority of trials, which is probably due to insufficient strength of the TA muscle on the affected side. In addition, the AFO may have hampered ankle dorsiflexion beyond 90 degrees.

With respect to the stance leg during SSS, between-group differences in EMG onsets and amplitudes were most pronounced in RF. The knee extensor moment generated by this muscle may contribute to the deceleration of walking.[28] In SSS, deceleration of walking would save time to make the additional stride in front of the obstacle. Hence, the delayed RF-stance onsets and reduced amplitudes (both initial and late) in the stroke group may indicate that they decelerate walking less effectively than controls. Ground reaction forces, however, are needed to provide conclusive evidence on the consequences of the RF-stance deficits in the persons with stroke.

The LSS was most frequently applied in the easier trials, with longer ARTs. In contrast to SSS, foot contact was postponed in LSS, and the foot was positioned after the obstacle. The increase in knee flexion angles that was observed during the obstacle crossing swing phase was less prominent in the participants with stroke than in the controls, which is likely related to their decreased BF-avoid amplitudes. High TA-avoid response amplitudes in the participants with stroke might be interpreted as part of a flexion synergy. Synergistic leg flexion may have assisted foot clearance with respect to the obstacle, where selective knee flexion failed. Furthermore, in order to lengthen the crossing stride, additional extensor activity has to be provided by the stance leg. This is presumably reflected in the large late response amplitudes of BF-stance, generating large hip extension moments.[28] In the participants with stroke, BF-stance response amplitudes tended to be smaller than in controls, which may have reduced trunk progression, which is in line with earlier reports.[29] This may have contributed to decreased[30] and often insufficient stride lengthening leading to more frequent landing of the heel on the rear end of the obstacle.

In spite of the clear kinematic differences between LSS and SSS, the muscle activation sequence was similar for both strategies, with BF-avoid and RF-stance being activated first and at high amplitudes. This observation is in agreement with previous research reporting an early and a later class of responses in order to adjust an ongoing movement of the arm[31] or leg.[32] The early, automatic response was modifiable in size but not in direction, whereas the later response changed the direction of movement according to the subjects' intention. In line with this reasoning, the initial responses in the current study may be interpreted as a fast, generic 'safety' response to the obstacle in order to retract the swing limb (BF-avoid) and slow down the ongoing hip extension of the stance limb (RF-stance). In contrast, the late muscle responses in the current study may be strategy-specific.

In the present study, the people with stroke demonstrated delayed responses to the obstacle, particularly in those muscles that are considered to be the prime movers. Previous research has also reported delayed onsets of step adjustments in people with stroke in response to a displacement of the stepping target.[9] It has been suggested that in healthy people these online step adjustments represent a special class of reflex-like responses that are faster than voluntary reactions[14] and may, therefore, be under automatic rather than cognitive control.[14, 32, 33] In this perspective, the delayed responses in the people with stroke suggest that they use different neural pathways for online step adjustments, which might involve cognitive control. This suggestion is supported by the observation that people with stroke needed disproportionate amounts of attention during obstacle crossing.[34]

In the control group, we observed similar early onset latencies for the left and right leg (i.e. BF-avoid and RF-stance). It suggests that the first, generic reaction to an obstacle involves bilateral coordinated responses, rather than independently organized unilateral responses. Particularly these primary responses were bilaterally delayed in the people with stroke. This finding may explain why the capacity to avoid sudden obstacles seems to be affected in people with stroke irrespective of whether the paretic or the non-paretic leg is used as the lead limb.[4] As a consequence, unilateral damage to the pathways involved in the avoidance response may necessitate people with stroke to resort to different (slower) neural circuits for the control of both legs.

A limitation of this study is that all but one participant in the stroke group wore an AFO, which complicated the interpretation of the TA-avoid and GM-avoid activity. Future studies should evaluate the ankle kinematics in persons with stroke who are not dependent on the use of an orthosis. Second, all post-stroke participants in this study were community walkers, which limits the generalizability to persons with poorer gait capacity. Nevertheless, our conclusions are pertinent because online step adjustments are particularly important for community-dwelling subjects. Third, we did not have brain images of our participants to identify the exact location of the brain lesions. Such knowledge might have been informative with regard to the neural pathways involved in the step adjustments. Finally, the findings on RF-stance activity call for further research including measurement of ground reaction forces during online gait adjustments.

Implications of the study

The current study explored the capacity of people with stroke to adapt an ongoing stride in response to a sudden obstacle. The results confirm previous research[4] that, even in people who were only mildly affected by stroke, gait adaptability is reduced, most prominently under time pressure. Some of the underlying impairments seem to involve both delayed and reduced activity of the prime movers, which coincides with essential kinematic changes that explain why participants with stroke are less able to adequately adjust their stride length in response to a sudden obstacle. This reduced gait adaptability may place people with stroke at a high risk of falling. Gait adaptability may improve with time-critical obstacle training, e.g. on a treadmill with visual objects projected on the belt[35] and, in post-stroke drop foot, with functional electrical stimulation.[16] Future research is needed to evaluate whether such training translates to safer community ambulation.

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Part 2

Training of dynamic balance and gait

Chapter 4

Effects of exercise therapy on balance capacity in chronic stroke: systematic review and meta-analysis

Published as

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Abstract

Background and objectives: The purpose of this systematic review and meta-analysis was to investigate the effects of exercise training on balance capacity in people in the chronic phase after stroke. Furthermore, we aimed to identify which training regimen was most effective.

Methods: Electronic databases were searched for randomized controlled trials (RCTs) evaluating the effects of exercise therapy on balance capacity in the chronic phase after stroke. Studies were included if they were of moderate or high methodological quality (PEDro score≥4). Data was pooled if a specific outcome measure was reported in at least three RCTs. A sensitivity analysis and consequent subgroup analyses were performed for the different types of experimental training (balance and/or weight-shifting training, gait training, multisensory training, high-intensity aerobic exercise training and 'other' training programs).

Results: Forty-three RCTs out of 369 unique hits were included. A meta-analysis could be conducted for the Berg Balance Scale (BBS, 28 studies, N=985), Functional Reach Test (FRT, 5 studies, N=153), Sensory Organization Test (SOT, 4 studies, N=173) and mean postural sway velocity (3 studies, N=89). A significant overall difference in favor of the intervention group was found for the BBS (mean difference (MD) 2.22 points (+3.9%); 95%CI 1.26-3.17;$p<0.01$;$I^2=52\%$), FRT (MD=3.12 cm;95%CI 0.90-5.35;$p<0.01$;$I^2=74\%$) and SOT (MD=6.77 (+7%) points;95%CI 0.83-12.7;$p=0.03$;$I^2=0\%$). Subgroup analyses of the studies that included BBS outcomes demonstrated a significant improvement following balance and/or weight-shifting training of 3.75 points (+6.7%;95%CI 1.71-5.78;$p<0.01$;$I^2=52\%$) and following gait training of 2.26 points (+4.0%;95%CI 0.94-3.58;$p<0.01$;$I^2=21$, while no significant effects were found for other training regimens.

Conclusion: This systematic review and meta-analysis showed that balance capacities can be improved by well-targeted exercise therapy programs in the chronic phase after stroke. Specifically, balance and/or weight-shifting and gait training were identified as successful training regimens.

Introduction

After stroke, a main goal of rehabilitation is to promote independence in activities of daily living (ADL). An important determinant of ADL performance is standing balance, which is a strong predictor of functional recovery[1, 2] and walking capacity[3, 4], and an important risk factor for falls[5] after stroke. Although the vast majority (75%) of people after stroke regain independent standing-balance capacity[6], weight-bearing asymmetry and increased postural sway often persist, as well as a diminished capacity to voluntarily shift body weight or to withstand external perturbations.[7] Hence, a key goal of rehabilitation treatment is to improve balance capacity, for which various types of exercise therapy are being used.[7]

Previous meta-analyses of the effects of exercise therapy on improving balance capacity have been inconclusive.[8-11] There appeared to be an effect of biofeedback training on postural sway and of repetitive task training on sit-to-stand activities[8], but both types of training did not result in better performance on clinical tests of balance capacity.[9] In addition, it remained unclear which type of training regimen would be most effective. Furthermore, previous meta-analyses did not address whether training effects differed between post-stroke stages. One systematic review reported that favorable effects of balance exercises were restricted to the chronic phase (≥6 months post onset), but a meta-analysis was not included to substantiate this statement.[12] Nevertheless, several studies that have been published since, suggest that exercise therapy may yield significant improvements in balance capacity in individuals in the chronic phase of stroke.[13, 14]

Evaluating the effects of exercise therapy in the chronic phase of stroke is of particular interest, as the results are unlikely to be influenced by spontaneous neurological recovery. Spontaneous recovery generally is apparent in the first two to three months after stroke[3, 15] and may demonstrate large heterogeneity across individuals.[8] However, on average, little if any further recovery is expected beyond six months after stroke.[16]

Therefore, the purpose of the present systematic review was to investigate the effects of exercise therapy on balance capacity in the chronic phase after stroke. We included articles on all types of training regimens that reported measures of balance capacity to evaluate training effects. Since we were particularly interested whether the type of intervention had a differential effect on gains in balance control, we conducted a subsequent sensitivity analysis. Interventions were categorized based on the type of training regimen (balance and/or functional weight-shifting training, gait training, multisensory training, high-intensity aerobic training and 'other' training programs) and we determined whether this categorization modified the overall effect. In addition, we examined whether there was an influence of intensity of training on balance capacity.

Methods

Definitions

According to the definition of the World Health Organization, we defined stroke as "rapidly developing signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent nonvascular cause".[17] Participants were in the chronic phase after stroke if they were six or more months post onset. A study was identified as a randomized controlled trial (RCT) if "the individuals (or other units) followed in the trial were definitely or possibly assigned prospectively to one of two (or more) alternative forms of healthcare using random allocation".[18] We defined exercise therapy as "a regimen or plan of physical activities designed and prescribed for specific therapeutic goals with the purpose to restore normal musculoskeletal function or to reduce pain caused by diseases or injuries" (Medline Subject Heading; MeSH). Training modalities using electrical devices such as treadmills are included in our definition, but not those using assistive devices such as canes, walkers, splints or functional electrical stimulation.

Balance capacity was defined as the ability to maintain, achieve or restore a state of balance during any posture.[19] This includes all different aspects of balance capacity as described in a model by Tyson et al., like static and dynamic balance, body alignment and weight distribution.[20] Balance outcomes included in this study should assess any of these aspects and should be validated and found reliable for individuals with stroke. Balance outcomes should measure at the ICF level of body functions and structures (such as posturography) or capacities/activities (such as the Berg Balance Scale).

Study Identification

We searched PubMed, Excerpta Medica Databank (EMBASE) and the Physiotherapy Evidence Database (PEDro) from 2000 to January 2015. Indexing terms and free-text words of the following key words were used: "postural balance" or "balance", and "chronic stroke" or "stroke" or "cerebrovascular accident", and "training" or "balance training" or "physical activity" or "physical therapy" or "rehabilitation", and "randomized controlled trial" or "RCT" or "randomized clinical trial" (STable.I, please see http://stroke.ahajournals.org). Studies were included if (1) the study population included adults (≥18 years of age), with a minimal time since stroke of 6 months for all included participants; (2) the design was an RCT; (3) the intervention studied was a form of exercise therapy; (4) at least one of the study outcomes evaluated balance capacity; (5) the study showed at least moderate to high methodological quality based on the PEDro score (see Quality appraisal); (6) the study was published in the English language. Bibliographies of selected studies were searched manually for additional relevant studies. The protocol of this review was not previously published. We adhered to the PRISMA guidelines.[21]

Quality appraisal

The Physiotherapy Evidence Database (PEDro) Scale[22, 23] (range 0-10) was used to assess methodological quality of the included studies. When a PEDro score was not available from the database, the study was scored by two reviewers independently (H.D. and M.P. or A.H.). In the case of disagreement, an additional assessment was done by a third reviewer (A.H. or M.P.). Studies were considered to be of 'high quality' when the PEDro score was ≥6 and of 'moderate quality' when the score was 4 or 5.[23] Studies with a score <4 points were excluded from further analysis.[9, 24, 25]

Meta-Analysis

For all selected studies, a stepwise categorization of the experimental training regimens was performed (see Supplementary figure 1, SFig.I). Five different categories were distinguished: (1) balance and/or functional weight-shifting training; (2) gait training; (3) training with altered sensory input (multisensory training); (4) high-intensity aerobic training; and (5) 'other' training programs. The classification process was based on hierarchical exclusion; a training intervention program was included in a specific category if its primary content (or added content compared to the control intervention) did not fit in the categories specified before.

From the selected studies, the following data was extracted: sample size, mean age of participants, mean time post stroke, type of study population (i.e. community dwelling people or inpatients), training duration, type of experimental and control training, and between-group differences in balance-specific outcome measures. If information was missing, we contacted the corresponding author.

Data was pooled when a particular outcome measure was used in at least three RCTs. We did not pool data between outcome measures, as the reported measures of balance capacity encompass a variety of abilities for maintaining, achieving or restoring a state of balance during any posture. Means and standard deviations (SD) of both the post-intervention and follow-up measurements were extracted from each study for both the experimental and control group. If a study did not report post-intervention scores, we asked the authors to provide these. When the authors could not be reached, we calculated the post-intervention outcomes by using the mean pre-intervention scores and the pre-post intervention difference, assuming equal variance. A summary effect size (SES) with 95% confidence interval (CI) was calculated based on the effect sizes (mean difference, MD) of the individual studies, calculated as Hedges' g. Between-study variation (statistical consistency) was assessed with the I^2 statistic.[19] Since heterogeneity between studies is expected, a random-effects model was used for all analyses.[26] A sensitivity analysis was performed for the type of experimental intervention, if this intervention type was investigated in at least 3 studies. When a significant effect was found, we conducted subgroup analyses to identify which intervention yielded improvement in balance outcome and to identify whether there was an intensity difference in time spent in exercise therapy between the experimental and control group. In addition, we investigated small-study effects (i.e. a trend for smaller studies to show larger treatment effects) by visual inspection of funnel plots. When asymmetry of funnel plots was observed, this was formally tested by Eggert's regression intercept and Duval & Tweedie's trim and fill. For all analyses, Comprehensive Meta Analysis (Biostat, Englewood, New Jersey) was used; two-tailed alpha was set at 0.05.

Results

Study Identification

After electronic search of the databases, 43 out of 369 unique hits met the inclusion criteria (figure 1). Supplementary table I (STable.I) shows the characteristics of the included RCT's. Twelve studies involved balance and/or functional weight-shifting training, 14 gait training, 7 multisensory training, 4 high-intensity aerobic exercises, and 6 'other' training regimens. Overall, the mean time post stroke ranged from 7 months to 7.7 years. The total training duration varied from 1.9 to 61.7 hours. Seven studies showed a difference in training intensity between the experimental and the control group, ranging from 4.5 to 61.7 hours. In five other studies, the control group did not receive any intervention. Twenty-two out of the 43 selected studies showed a significant between-group difference for at least one of the outcome measures reported. This was the case for 11 out of 12 balance and/or functional weight-shifting training studies, 7 out of 14 gait training studies, 2 out of 7 multisensory training studies, none of the high intensity aerobic exercise training studies, and 3 out of 6 of the studies with 'other' training regimens.

Quality Appraisal

Three studies were excluded from further analysis because of a PEDro score<4 (high risk of bias). PEDro scores of the included studies varied from 4 to 9 (STable.II). Of all included studies, 34 studies showed high quality and 9 moderate quality.

Meta – Analysis

A total of 21 different outcome measures were used (figure 1). Pooling of results was possible for the Berg Balance Scale (BBS) (n=28), Functional Reach Test (FRT) (n=5), Sensory Organisation Test (SOT) (n=4), and postural sway velocities while standing with eyes open (n=3). One of the studies reporting BBS scores did not include an immediate post-intervention measurement, but merely reported follow-up scores.[27] This study could therefore only be used in the follow-up analysis. One study did not report post-intervention scores, but merely pre-post intervention differences.[28] Unfortunately, we could not get in contact with the authors of this study. Therefore, the post intervention outcomes were calculated by using the mean pre-intervention scores and the pre-post intervention difference.

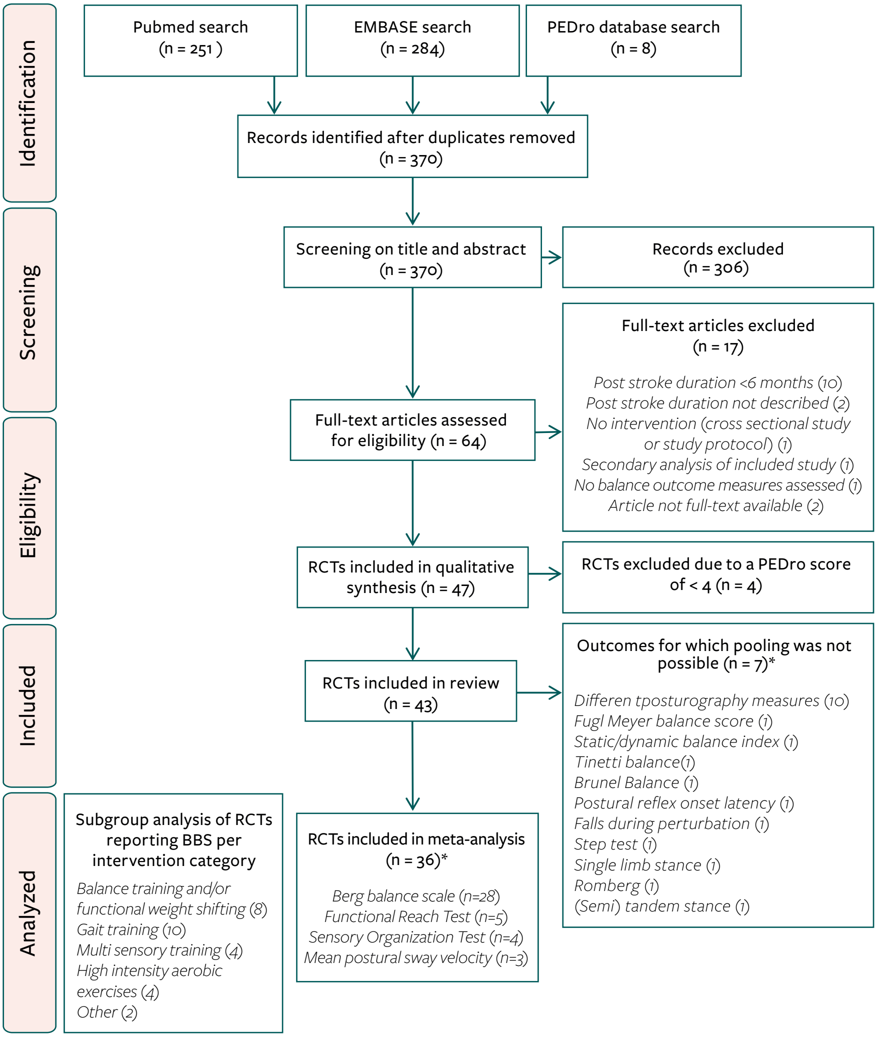


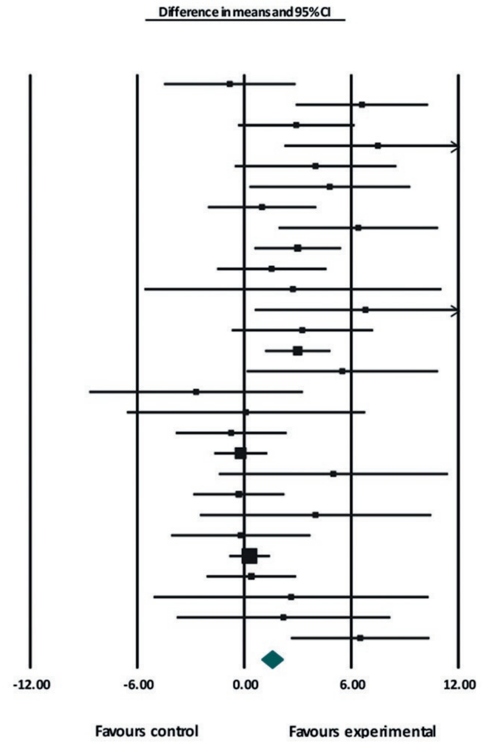
Figure 1 PRISMA flow diagram.

RCTs, randomized controlled trials; EMBASE, Excerpta Medica Database; PEDro Pysiotherapy evidence database; BBS, Berg Balance Scale; COP, Center of Pressure. * Note that some studies report more than one outcome measure.

4

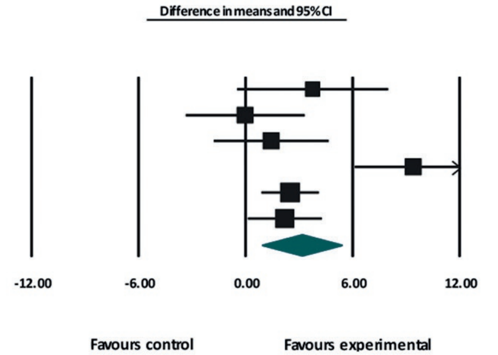
BBS post intervention

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Expermental	Control
	Statistics for each study							Sample size	
Cho KH 2012	-0.810	1.896	3.593	-4.525	2.905	-0.427	0.669	11	11
Farqalit 2013	6.600	1.906	3.633	2.864	10.336	3.463	0.001	20	20
Kim 2009	2.920	1.682	2.831	-0.378	6.218	1.736	0.083	12	12
Lee 2014	7.500	2.691	7.243	2.225	12.775	2.787	0.005	10	11
Lee 2012	4.000	2.329	5.423	-0.564	8.564	1.718	0.086	20	20
Llorens 2014	4.800	2.316	5.365	0.260	9.340	2.072	0.038	10	10
Marigold 2005	1.000	1.562	2.439	-2.061	4.061	0.640	0.522	22	26
Noh 2008	6.400	2.296	5.273	1.899	10.901	2.787	0.005	10	10
Chen 2014	3.000	1.255	1.575	0.541	5.459	2.391	0.017	15	15
Cho 2014	1.540	1.578	2.490	-1.553	4.633	0.976	0.329	15	15
Dias 2007	2.730	4.261	18.159	-5.622	11.082	0.641	0.522	20	20
Globas 2012	6.800	3.185	10.143	0.558	13.042	2.135	0.033	18	18
Middleton 2014	3.260	2.036	4.147	-0.731	7.251	1.601	0.109	19	19
Page 2008	3.000	0.948	0.898	1.142	4.858	3.165	0.002	4	3
Wang 2015	5.500	2.754	7.586	0.102	10.898	1.997	0.046	25	26
Westlake 2009	-2.700	3.070	9.425	-8.717	3.317	-0.879	0.379	8	8
Wu 2014	0.100	3.422	11.709	-6.607	6.807	0.029	0.977	14	14
Yen 2008	-0.730	1.599	2.558	-3.865	2.405	-0.456	0.648	7	7
Brogardh 2012	-0.200	0.773	0.597	-1.715	1.315	-0.259	0.796	16	15
Cha 2014	5.000	3.291	10.829	-1.450	11.450	1.519	0.129	10	10
Lau 2012	-0.300	1.318	1.738	-2.884	2.284	-0.228	0.820	41	41
Marin 2013	4.000	3.324	11.048	-2.515	10.515	1.203	0.229	11	9
Chu 2004	-0.200	2.004	4.018	-4.129	3.729	-0.100	0.921	7	5
Jin 2012	0.300	0.594	0.353	-0.865	1.465	0.505	0.614	68	65
Pang 2005	0.400	1.294	1.676	-2.137	2.937	0.309	0.757	32	31
Quaney 2009	2.630	3.948	15.588	-5.108	10.368	0.666	0.505	19	19
Immink 2014	2.200	3.070	9.426	-3.818	8.218	0.717	0.474	11	11
Pandian 2014	6.500	1.994	3.978	2.591	10.409	3.259	0.001	20	19
	1.519	0.291	0.085	0.949	2.090	5.220	0.000	495	490



FRT post intervention

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Expermental	Control
	Statistics for each study							Sample size	
Pandian 2014	3.760	2.177	4.739	-0.507	8.027	1.727	0.084	20	19
Hung 2014	-0.020	1.716	2.944	-3.383	3.343	-0.012	0.991	13	15
Kim 2013	1.440	1.659	2.751	-1.811	4.691	0.868	0.385	9	9
Cho 2012	9.400	1.688	2.849	6.092	12.708	5.569	0.000	15	13
Kang 2012 E1 vs C	2.500	0.835	0.698	0.863	4.137	2.992	0.003	10	10
Kang 2012 E2 vs C	2.200	1.074	1.154	0.095	4.305	2.048	0.041	10	10
	3.120	1.131	1.279	0.903	5.336	2.759	0.006	77	76



SOT post intervention

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Expermental	Control
	Statistics for each study							Sample size	
Chen 2014	5.633	63.752	4064.292	-119.318	130.585	0.088	0.930	15	15
Au-Yeung 2009	6.833	3.610	13.035	-0.243	13.910	1.893	0.058	56	52
Bonan 2004	8.667	9.042	81.754	-9.055	26.388	0.959	0.338	10	10
Tankisheva 2014	5.350	7.087	50.220	-8.540	19.240	0.755	0.450	7	8
	6.765	3.027	9.165	0.832	12.699	2.235	0.025	88	85

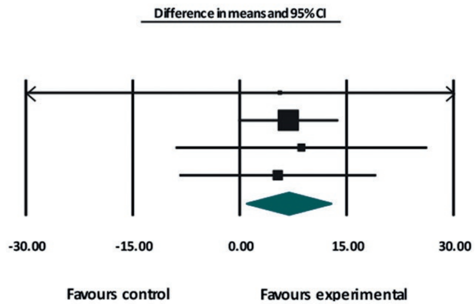


Figure 2 Summary effect sizes immediately post intervention for studies reporting Berg Balance Scale, Functional Reach Test and Sensory Organization Test.

BBS, Berg Balance Scale; FRT, Functional Reach Test; SOT, Sensory Organization Test. E1, experimental group 1; E2, experimental group 2; C, control group. The diamond is the summary effect size.

4

Pooling of studies for the immediate post-intervention effects showed a significant summary effect size in favor of the intervention group for the BBS (28 studies; N=985;MD=2.22 points [random];95%CI 1.26-3.17;$p<0.01$;$I^2=52\%$; figure 2 and STable.III), the FRT (5 studies;N=153;MD=3.12 cm [random];95%CI 0.90-5.35;$p<0.01$;$I^2=74\%$;figure 2), and the SOT (4 studies; N=173;MD=6.77% [random];95%CI 0.83-12.7;p=0.03;$I^2=0\%$;figure 2). Non-significant SES were found for postural sway velocities (3 studies;N=89; anterior-posterior direction MD=0.57 mm/s [random];95%CI -1.18-2.31;p=0.52;$I^2=74\%$; medio-lateral direction MD=0.82 mm/s [random];95%CI -2.55-4.20;p=0.63;$I^2=91\%$;SFig.II). Eleven studies reported follow-up data, with a time range after termination of the intervention of 1 to 5 months. Pooling showed significant SES after retention, favoring the intervention group, for the BBS (8 studies;N=338;MD=1.65 points [random];95%CI 0.22-3.07;p=0.02;$I^2=0\%$;-figure 3) and the SOT (3 studies;N=151;MD=3.91% [random];95%CI 0.10-7.73;p=0.04;$I^2=0\%$;-figure 3).

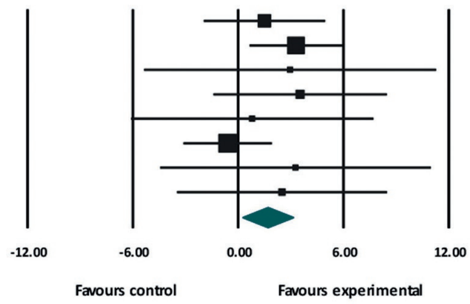
Sensitivity analysis, which could only be conducted for the immediate post-intervention measurement of the BBS, yielded a significant effect of intervention type (p=0.02). Subgroup analyses for the various types of experimental interventions (SFig.III, please see http://stroke.ahajournals.org) showed significant SES for balance and/or functional weight-shifting training (8 studies;MD=3.75 points [random];95%CI 1.71-5.78; $p<0.01$;$I^2=52\%$), and gait training (10 studies;MD=2.26 points [random];95%CI, 0.94-3.58; $p<0.01$;$I^2=21\%$). Nonsignificant SES were found for multisensory training (4 studies;MD=0.38 points [random];95%CI, -1.32-2.08;p=0.66;$I^2=22\%$) and high-intensity aerobic training (4 studies; MD=0.32 points [fixed];95%CI, -0.69-1.34;p=0.53;$I^2=0\%$).

The induced gains in BBS scores were not modified by between-group differences in intensity of training (p=0.18). The overall post intervention effects were modified by small studies, but the SES remained significant (MD=1.04 points [random];95%CI 0.03-2.06; after imputation of 9 studies, Eggert's regression intercept p-value<0.01; SFig.IV). Meta regression of PEDro score on immediate post intervention differences in means for the BBS studies did not show any modifying effects (28 studies;slope=0.03 [fixed];95%CI -0.27 – 0.32;p=0.85; SFig.V).

BBS follow-up

Study name	Statistics for each study							Sample size	
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Expermental	Control
Marigold 2005	1.500	1.779	3.164	-1.986	4.986	0.843	0.399	19	23
Chen 2014	3.300	1.368	1.873	0.618	5.982	2.411	0.016	15	15
Dias 2007	2.960	4.261	18.159	-5.392	11.312	0.695	0.487	20	20
Middleton 2014	3.530	2.537	6.437	-1.443	8.503	1.391	0.164	15	16
Wu 2014	0.800	3.535	12.498	-6.129	7.729	0.226	0.821	14	14
Lau 2012	-0.600	1.303	1.697	-3.153	1.953	-0.461	0.645	41	41
Quaney 2009	3.270	3.950	15.606	-4.473	11.013	0.828	0.408	19	19
Schmid 2012	2.500	3.070	9.424	-3.517	8.517	0.814	0.415	37	10
	1.649	0.725	0.526	0.227	3.071	2.273	0.023	180	158

Difference in means and 95% CI



SOT follow-up

Study name	Statistics for each study							Sample size	
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Expermental	Control
Chen 2014	2.950	2.527	6.386	-2.003	7.903	1.167	0.243	15	15
Au-Yeung 2009	5.300	3.499	12.244	-1.558	12.158	1.515	0.130	56	52
Tankisheva 2014	5.400	6.255	39.131	-6.860	17.660	0.863	0.388	6	7
	3.915	1.947	3.790	0.099	7.731	2.011	0.044	77	74

Difference in means and 95% CI

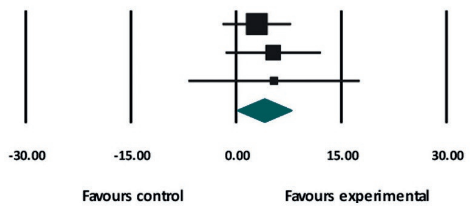


Figure 3 Summary effect sizes of follow up for studies reporting Berg Balance Scale and Sensory Organization Test.

BBS, Berg Balance Scale; SOT, Sensory Organization Test. The diamond is the summary effect size.

4

Discussion

This systematic review included 43 trials to assess the effects of exercise therapy on balance capacity in people in the chronic phase after stroke. Meta-analyses showed an overall improvement on several clinical balance tests (BBS, FRT and SOT) following exercise therapy. The sensitivity analysis with subsequent subgroup analyses of the BBS data, however, showed that significant improvements were restricted to balance and/or functional weight-shifting training and gait training. Importantly, the induced gains in BBS scores were not influenced by differences in the intensity of training applied between experimental and control arm of included trials. By specifically focusing on studies conducted in the chronic phase after stroke, the present meta-analysis convincingly demonstrates that exercise therapy may induce gains in balance capacity.

The present meta-analysis showed ambiguous results for outcomes on the level of body functions and structures (SOT; posturography measures), but yielded significant improvements following exercise therapy in outcome measures on the ICF level of activities (BBS; FRT). This finding suggests that the observed improvements in balance capacity are most likely due to optimization of compensatory balance control strategies, such as strengthening of ankle and hip strategies on the non-paretic side, improvement of trunk control, optimization of stepping strategies, and a more general adjustment of motor responses to altered sensory input and body dynamics.[7] Yet, it has to be noted that the meta-analyses at the level of body functions and structures were limited by the number of studies that used the same outcome measure (SOT, n=4; postural sway velocity, n=3). In the 43 studies that met our inclusion criteria, we identified a myriad of other measures at this ICF level, sometimes within a single study, that often yielded an inconsistent pattern of results.

An important finding of the present work is that the beneficial effect of exercise therapy was restricted to balance and/or functional weight-shifting and gait training. The finding that gait training was also effective in improving balance capacities may seem somewhat surprising, in light of the critical importance of *task-specificity* of exercise therapy after stroke.[25, 29] Yet, upon closer inspection (STable.III), the individual gait training studies that did not yield improvements in BBS scores mainly involved treadmill training with (partial) body weight support or robotic gait training with pelvic stabilization, which procedures greatly assist in controlling upright balance during walking. In contrast, the gait training studies that did report improvements in BBS scores often involved additional challenges to balance control during walking, such as walking on a treadmill while interacting with a virtual reality environment or walking while making turning movements. These observations therefore suggest that, for gait training to be effective in improving balance capacity, it is crucial to include challenging walking exercises, preferably without reduction in degrees of freedom by, for instance, an exoskeleton around the pelvis in robotic gait trainers, or by a harnessed body-weight support.[30]

Yet, establishing the mutual effectiveness of various gait training modalities on balance capacity remains an important subject for future research.

The question arises whether the beneficial effects of balance and/or functional weight-shifting training and of gait training can be explained by additional improvement of balance capacities (on top of the level achieved at the end of primary rehabilitation), or whether it reflects the reacquisition of skills that have been lost since the cessation of the primary rehabilitation process (due to inactivity and related 'disuse'[31]). Consistent with the latter notion, a previous study[32] investigating a community-based adaptive physical activity program for people with chronic stroke reported an average decline in BBS score of 1.5 points in the inactive control group over a period of six months. On the other hand, the plateau phase that is commonly reached about six months post stroke onset may also be due to saturation of the training regimens used during primary rehabilitation.[33] This saturation may be overcome by introducing new types of training (e.g. dynamic and challenging balance training, including balance perturbations, dual tasks and/or gait adaptability exercises) that exploit residual (latent) recovery potential.[33] In favor of this latter notion, the studies in the balance and/or functional weight-shifting training category showed on average 1.6-3.3 points improvement in BBS score in the active control condition, but yielded superior improvements in the experimental intervention groups. Future research is needed to definitively address the mechanisms underlying training-induced balance gains in the chronic phase of stroke.

The presently applied hierarchical classification of training regimens allowed us to group interventions that included the same type of exercises and to evaluate - in a sensitivity analysis - their combined effects on BBS scores relative to other intervention types. It must be mentioned, though, that this method of categorization still left a substantial degree of heterogeneity in the content of the interventions categorized. For example, the interventions in the balance and/or functional weight-shifting group, varied from circuit class training focusing on agility and dynamic balance control[34] to hydro-therapy-based tai-chi exercises[35]. Similarly, the control interventions were heterogeneous in nature as well. Due to this heterogeneity within the relatively small number of studies per group (n=8 for balance and/or functional weight-shifting training and n=10 for gait training), it is not possible to determine whether all forms of balance, functional weight-shifting or gait exercises included in these categories were equally effective. Thus, we recommend future research to focus on the identification of optimal forms of exercise therapy for improving standing balance in the chronic phase post stroke.

This systematic review and meta-analysis was limited by the number of studies included, particularly in the subgroup analyses, which may have resulted in a type II error (i.e. false-negative outcome). We considered including studies with an *average* time post onset of more than 6 months that did *not* exclusively recruit participants in the chronic phase after stroke. This would have borne the risk, however, of our results being confounded by differential effects of training in the various post-stroke phases. We therefore decided to adhere to a rigorous inclusion criterion regarding the minimal time post stroke. In addition, balance capacities after stroke can be influenced by stroke severity and stroke location.[7] Both factors, however, were not systematically reported in the included RCTs and we therefore could not determine the impact of stroke location and stroke severity on the effects of balance training. Another limitation was the variety of outcome measures used in the literature, which restricted the number of studies that could be considered in the meta-analysis. Furthermore, the finding that differences in training intensity between experimental and control groups were not identified as an effect modifier in the present study should be interpreted cautiously, because this analysis was possibly underpowered due to the small number of studies.

Finally, the use of the BBS in our sensitivity analysis also comes with a limitation, as this outcome measure has a ceiling effect particularly in the chronic phase after stroke.[36] Indeed, 12 out of 28 studies reported near-normal BBS scores (50-56 points) in their intervention groups directly following exercise therapy; in the control groups, this was true for only 6 out of 28 studies. These ceiling effects may have resulted in an underestimation of therapy effects in the higher-functioning individuals, which effect seems to explain - at least partly - the relatively modest gains on the BBS. Importantly, ceiling effects do not appear to account for the differential effects between intervention types, as revealed by the sensitivity analysis. The mean baseline BBS score across studies was below 48 points for each intervention type, and there were only 5 out of 28 studies reporting BBS scores of more than 50 points (divided over 3 intervention types). This leaves sufficient room for improvement and, therefore, cannot explain the lack of training-induced gains following multisensory and aerobic training. Yet, for future studies evaluating training effects in high-functioning stroke survivors, we recommend to use a different primary outcome on the ICF level of activities. One such alternative may be the mini-Balance Evaluation System Test (mini-BESTest), which is a test of dynamic balance that has shown high reliability and a lower ceiling effect than the BBS in people after stroke.[37, 38]

Conclusion

Our systematic review and meta-analysis shows that balance capacity can be improved by exercise therapy in the chronic phase after stroke. Specifically, balance and/or functional weight-shifting training and gait training were identified as successful training regimens. We therefore recommend exercise therapy for people in the chronic phase after stroke for improving balance capacities, provided that training regimens include exercises targeting balance, weight-shifting and/or gait.

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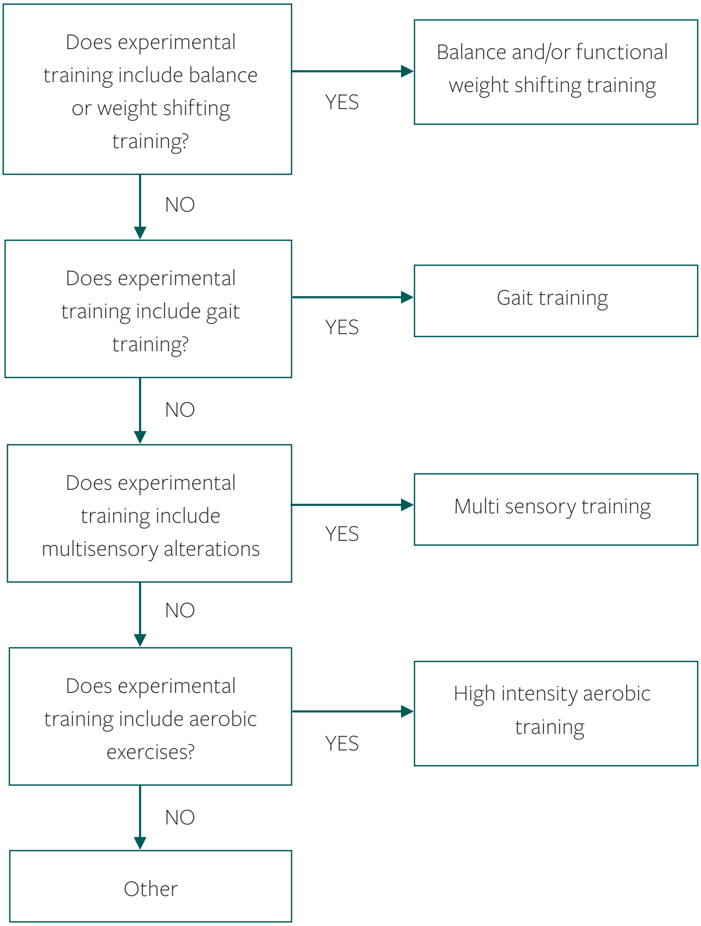
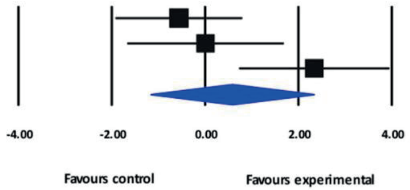
Supplementary figures



Supplementary Figure I (SFig.1) Stepwise process of intervention categorization.

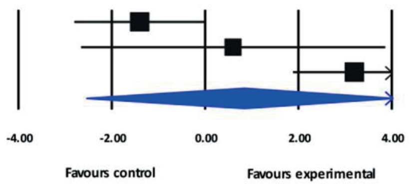
Postural sway AP post intervention

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Expermental	Control
	Statistics for each study							Sample size	
Cho KH 2012	-0.560	0.698	0.487	-1.928	0.808	-0.803	0.422	11	11
Cho 2014	0.010	0.860	0.739	-1.675	1.695	0.012	0.991	15	15
Choi 2014	2.340	0.827	0.684	0.719	3.961	2.830	0.005	19	18
	0.568	0.891	0.794	-1.179	2.314	0.637	0.524	45	44



Postural sway ML post intervention

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Expermental	Control
	Statistics for each study							Sample size	
Cho KH 2012	-1.400	0.719	0.517	-2.809	0.009	-1.948	0.051	11	11
Cho 2014	0.600	1.667	2.780	-2.668	3.868	0.360	0.719	15	15
Choi 2014	3.200	0.675	0.456	1.877	4.523	4.740	0.000	19	18
	0.822	1.722	2.965	-2.553	4.196	0.477	0.633	45	44

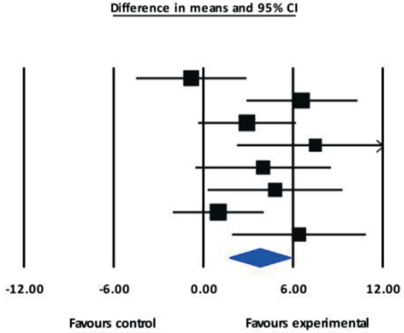


Supplementary Figure II (SFig.II) Summary effect sizes immediately post intervention for studies reporting mean postural sway in anterior-posterior and medial-lateral direction.

AP, anterior-posterior; ML medial-lateral. The blue diamond is the summary effect size.

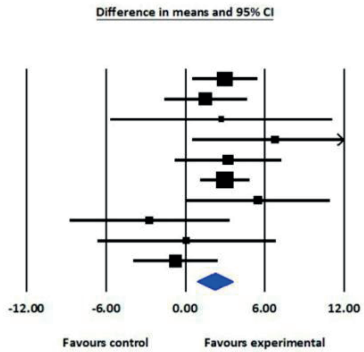
BBS post intervention | experimental: balance

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Sample size: Experimental	Sample size: Control
Cho KH 2012	-0.810	1.896	3.593	-4.525	2.905	-0.427	0.669	11	11
Farqalit 2013	6.600	1.906	3.633	2.864	10.336	3.463	0.001	20	20
Kim 2009	2.920	1.682	2.831	-0.378	6.218	1.736	0.083	12	12
Lee 2014	7.500	2.691	7.243	2.225	12.775	2.787	0.005	10	11
Lee 2012	4.000	2.329	5.423	-0.564	8.564	1.718	0.086	20	20
Llorens 2014	4.800	2.316	5.365	0.260	9.340	2.072	0.038	10	10
Marigold 2005	1.000	1.562	2.439	-2.061	4.061	0.640	0.522	22	26
Noh 2008	6.400	2.296	5.273	1.899	10.901	2.787	0.005	10	10
	3.747	1.039	1.080	1.710	5.784	3.605	0.000	115	120



BBS post intervention | experimental: gait

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Sample size: Experimental	Sample size: Control
Chen 2014	3.000	1.255	1.575	0.541	5.459	2.391	0.017	15	15
Cho 2014	1.540	1.578	2.490	-1.553	4.633	0.976	0.329	15	15
Dias 2007	2.730	4.261	18.159	-5.622	11.082	0.641	0.522	20	20
Globas 2012	6.800	3.185	10.143	0.558	13.042	2.135	0.033	18	18
Middleton 2014	3.260	2.036	4.147	-0.731	7.251	1.601	0.109	19	19
Page 2008	3.000	0.948	0.898	1.142	4.858	3.165	0.002	4	3
Wang 2015	5.500	2.754	7.586	0.102	10.898	1.997	0.046	25	26
Westlake 2009	-2.700	3.070	9.425	-8.717	3.317	-0.879	0.379	8	8
Wu 2014	0.100	3.422	11.709	-6.607	6.807	0.029	0.977	14	14
Yen 2008	-0.730	1.599	2.558	-3.865	2.405	-0.456	0.648	7	7
	2.260	0.675	0.456	0.936	3.583	3.346	0.001	145	145



Supplementary Figure III (SFig.III) Summary effect sizes of subgroup analysis for intervention type.

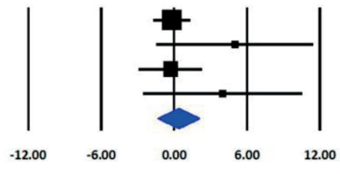
BBS, Berg Balance Scale; experimental, intervention type. The blue diamond is the summary effect size.

Favours control Favours experimental

BBS post intervention | experimental: multisensory

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Experimental	Control
	Statistics for each study							*Sample size*	
Brogardh 2012	-0.200	0.773	0.597	-1.715	1.315	-0.259	0.796	16	15
Cha 2014	5.000	3.291	10.829	-1.450	11.450	1.519	0.129	10	10
Lau 2012	-0.300	1.318	1.738	-2.884	2.284	-0.228	0.820	41	41
Marin 2013	4.000	3.324	11.048	-2.515	10.515	1.203	0.229	11	9
	0.377	0.868	0.753	-1.324	2.078	0.434	0.664	78	75

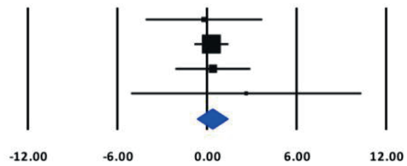
Difference in means and 95% CI



BBS post intervention | experimental: aerobic

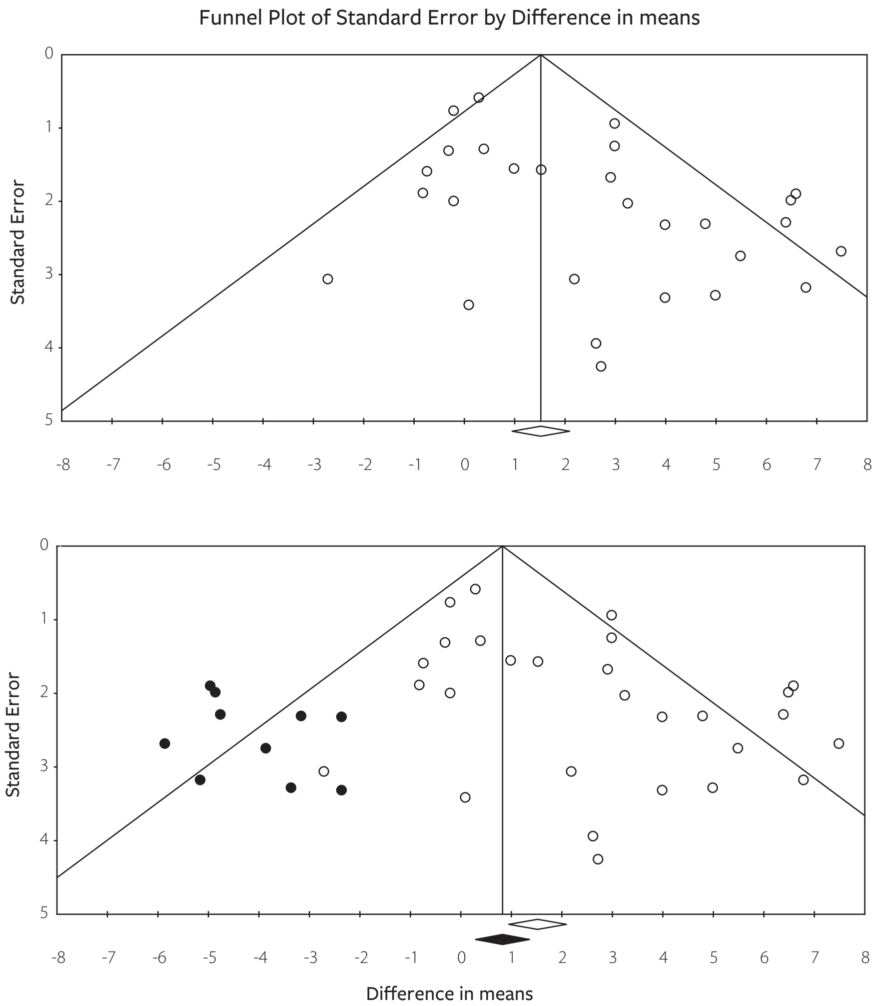
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Experimental	Control
	Statistics for each study							*Sample size*	
Chu 2004	-0.200	2.004	4.018	-4.129	3.729	-0.100	0.921	7	5
Jin 2012	0.300	0.594	0.353	-0.865	1.465	0.505	0.614	68	65
Pang 2005	0.400	1.294	1.676	-2.137	2.937	0.309	0.757	32	31
Quaney 2009	2.630	3.948	15.588	-5.108	10.368	0.666	0.505	19	19
	0.323	0.517	0.267	-0.690	1.336	0.624	0.533	126	120

Difference in means and 95% CI

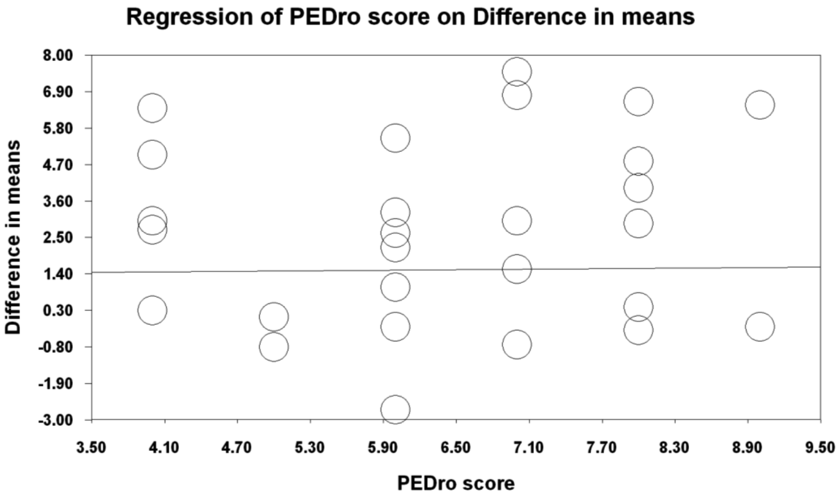


Supplementary Figure III (SFig.III) Continued

BBS, Berg Balance Scale; experimental, intervention type. The blue diamond is the summary effect size.



Supplementary Figure IV (SFig.IV) Funnel plots for assessing small study effects of all included studies reporting Berg Balance Scale (A), and after imputation (black dots and square, B).



Supplementary Figure V (SFig.V) Meta regression of PEDro scores on immediate post intervention differences in means all included studies reporting Berg Balance Scale.

Supplementary Tables

Supplementary Table I (S.TableI) Pubmed Search Strategy

	Postural Balance"[Mesh] OR ("postural balance"[MeSH Terms] OR ("postural"[All Fields] AND "balance"[All Fields]) OR "postural balance"[All Fields]) OR ("Balance"[Journal] OR "balance"[All Fields])"
AND	("Stroke"[Mesh] OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR ("cerebrovascular"[All Fields] AND "accident"[All Fields]) OR "cerebrovascular accident"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields]) OR (chronic[All Fields] AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])))
AND	("Exercise"[Mesh] OR ("physical therapy modalities"[MeSH Terms] OR ("physical"[All Fields] AND "therapy"[All Fields] AND "modalities"[All Fields]) OR "physical therapy modalities"[All Fields] OR ("physical"[All Fields] AND "therapy"[All Fields]) OR "physical therapy"[All Fields]) OR ("rehabilitation"[Subheading] OR "rehabilitation"[All Fields] OR "rehabilitation"[MeSH Terms]) OR ("education"[Subheading] OR "education"[All Fields] OR "training"[All Fields] OR "education"[MeSH Terms] OR "training"[All Fields]) OR (("Balance"[Journal] OR "balance"[All Fields]) AND ("education"[Subheading] OR "education"[All Fields] OR "training"[All Fields] OR "education"[MeSH Terms] OR "training"[All Fields])) OR ("motor activity"[MeSH Terms] OR ("motor"[All Fields] AND "activity"[All Fields]) OR "motor activity"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]))
AND	("Randomized Controlled Trial"[Publication Type] OR ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]) OR RCT[All Fields] OR ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized clinical trial"[All Fields] OR "randomised clinical trial"[All Fields]))
AND	English[lang]

Supplementary Table II (S.TableII) Extracted research evidence of the included RCTs

Study	PEDro score	Sample Size (E/C)*, pre- and post intervention	Age mean ± SD (years)	Time since stroke mean ± SD	Study population
Balance and/or functional weight shifting training					
Au-Yeung et al. (2009)[1]	6	pre: 136 (74/62) post: 108 (56/52)	E: 61.7±10.7 C: 65.9±10.5	E: 54±79 mo C: 64±106 mo	Community dwelling
Cho KH et al. (2012)[2]	5	pre: 24 (12/12) post: 22 (11/11)	E:65.3±8.4 C:63.1±6.9	E:13±3mo C:13±3mo	Unknown
Farqalit et al. (2013)[3]	8	40 (20/20), no attrition	E:58.7±4.2 C: 60.1±4.8	E: 2.6±1.1 y C: 2.7±0.9 y	Unknown
Gok et al. (2008)[4]	6	30 (15/15), no attrition	E: 55.1±11.4 C: 59.7±4.8	E: 15±3 mo C: 21±4 mo	Inpatient rehabilitation
Hung et al (2014)[5]	7	pre: 30 (15/15) post: 28 (13/15)	E: 55.4±10.0 C: 53.4±10.0	E: 21±11 mo C: 15±8 mo	Outpatient rehabilitation
Kim et al. (2013)[6]	6	pre: 30 (10/10/10) post: 27 (9/9/9)	E1:55.3 ±12.1 E2:54.8± 8.8 C: 59.8±8.9	E1:8 ±3 mo E2:7± 1 mo C: 9±4 mo	Inpatient rehabilitation
Kim et al. (2009)[7]	6	24 (12/12), no attrition	E: 52.4±10.1 C: 51.8±7.1	E: 26±10 mo C: 24±9 mo	Unknown
Lee et al. (2014)[8]	7	21(10/11) no attrition	E: 47.9±12.0 C:54.0±11.9	E: 12±5 mo C: 11±5 mo	Unknown
Lee et al. (2012)[9]	8	40 (20/20) no attrition	E: 53.8±11.3 C: 54.1±11.1	E: 13±6 mo C: 14±6 mo	Unknown

Training duration	Control training	Experimental training	Balance Outcome	Between-group difference†
E/C: 1 hour, once a week, 12 weeks HE: 3 hours a week	General exercise program: breathing, stretching, active mobilization and cognitive exercises	Short form Tai Chi	End-point CoG excursion SOT	+ +/=‡
E/C: 60 minutes, 5 days per week, 6 weeks. E: 30 min, 3 times a week, 6 weeks.	Standard rehabilitation program with PT and OT, if appropriate ST.	Additional Virtual reality balance training on a Wii Fit balance board	BBS ML and AP postural sway velocity (eyes open and closed)	+ =
E/C: 100 repetitions, 5 days a week, 4 weeks	Sit tot stand training with a symmetrical foot position, next to a supervised exercise programme (stretching and strengthening exercises and balance and gait training)	Sit to stand training with asymmetrical foot positioning (affected foot behind the unaffected foot), next to a supervised exercise programme (stretching and strengthening exercises and balance and gait training)	BBS	+
E/C: 2-3 hours, 5 times a week, 4 weeks E: 20 min, 5 times a week, 4 weeks	Conventional stroke rehabilitation, spasticity inhibition, PT, OT and speech therapy.	Control training with additional weight shifting exercises on Kinesthetic Ability Trainer (KAT)	Static balance index Dynamic balance index FM balance score	+ + +
E/C: 30 minutes, 2 times per week, 12 weeks.	Routine rehabilitation training plus conventional weight shift training	Routine rehabilitation training plus Wii Fit training	Stability index FRT	+/=# +
E/C: 2x30 min, 5 times a week, 4 weeks E1+2: 30 min, 5 times a week, 4 weeks	Trunk control, dynamic balance and weight shifting training	E1: 20min video, 10 min sitting and standing balance exercise	FRT	=
E/C: 40 min , 4 times a week, 4 weeks E: 30 min , 4 times a week, 4 weeks_	Conventional PT: gait training and weight shifting	Control training with additional virtual reality training balance, weight shifting and stepping	BBS Static CoP displacement Dynamic CoP displacement	+ = +
E/C: 30 min, 7 times a week, 4 weeks E: 30 min, 3 times a week, 4 weeks	Conventional PT	Control training with additional augmented-reality postural control training	BBS	=
E/C: 1 hour, 5 times a week, 4 weeks E: 20 min, 5 times a week, 4 weeks	Conventional PT	Additional weight shifting exercises with balance control trainer (BCT)	BBS	+

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Supplementary Table II (S.TableII) Continued

Study	PEDro score	Sample Size (E/C)*, pre- and post intervention	Age mean ± SD (years)	Time since stroke mean ± SD	Study population
Balance and/or functional weight shifting training					
Llorens et al. (2015)[10]	8	20 (10/10)	E: 58.3±11.6 C: 55.0±11.6	E: 13 ±8 mo C: 19±7 mo	Outpatient rehabilitation
Marigold et al. (2005)[11]	6	pre: 61 (30/31) post: 48 (22/26)	E: 68.1±9.0 C: 67.5±7.2	E: 3.6±2 y C: 3.8±2 y	Community dwelling
Noh et al. (2008)[12]	4	pre: 25 (13/12) post: 20 (10/10)	E: 61.9±10.1 C:66±11.4	E: 2.8±4 y C: 1.6±2 y	Community dwelling
Gait training					
Chen et al. (2014)[13]	7	pre: 31 (15/16) post: 30 (15/15)	E: 53.7±11.1 C: 54.8±8.1	E: 2.9±2 y C: 2.2±2 y	Unknown
Cho et al. (2014)[14]	7	Pre: 32 (16/16) Post: 30 (15/15)	E:65.9±5.7 C:63.5±5.5	E14± 5 mo C: 15±6mo	Unknown
Cho et al. (2013)[15]	6	28 (15/13), no attrition	E: 53.9±12.6 C: 53.9±12.4	E:45±20 mo C: 46±17 mo	Inpatient rehabilitation
Dias et al. (2007)[16]	4	40 (20/20)	E: 70.4±7 C:68.0±11	E: 47±64 mo C: 49±30 mo	Unkown
Globas et al. (2012)[17]	7	pre: 38 (20/18) post: 36 (18/18)	E: 68.6±6.7 C:68.7±6.1	E: 60±47 mo C: 70±67 mo	Community dwelling
Kang et al. (2012)[18]	7	pre: 32 (11/11/10) post: 30 (10/10/10)	E1: 55.9±6.5 E2: 56.3±7.6 C: 56.1±7.8	E1: 14±4 mo E2: 14±4 mo C: 15±7 mo	Unknown
Middleton et al. (2014)[19]	6	pre: 43 (23/20) post: 38 (19/19) follow-up: 31 (15/16)	E: 61.4±15.7 C: 60.7±11.4	E: 50±57 mo C: 29±24 mo	Unknown

Training duration	Control training	Experimental training	Balance Outcome	Between-group difference†
E/C: 1 hour, 5 times a week, 4 weeks	1 hour of conventional PT: static and dynamic balance exercises and walking exercises	30 minutes of control training and 30 minutes of virtual reality based step exercises	BBS Tinetti Balance Brunel Balance	+ -
E/C: 1 hour, 3 times a week, 10 weeks	Stretching and weight shifting exercises	Circuit training with agility, dynamic balance and multisensory exercises	BBS Postural reflex onset latency Falls during perturbation	= + +
E/C: 1 hour, 3 times a week, 8 weeks	Gym exercise program: gait training and strengthening exercises	Aquatic therapy, based on TAi Chi and Halliwick methods	BBS	+
E/C: 40 min, 12 sessions in 4 weeks	Standard treadmill training and general exercise program	Turning-based treadmill training and general exercise program	BBS SOT LOS	+ +/=** +/=††
E/C: 30 min, 3 times a week, 6 weeks. *Standard rehabilitation:* E/C: 80 minutes, 5 times a week, 6 weeks.	Additional walking on a treadmill, next to standard rehabilitation program with PT, OT and FES.	Additional treadmill training based real-world video recording, next to standard rehabilitation program with PT, OT and FES.	BBS ML and AP postural sway velocity PSVM	
E/C: 30 min, 3 times a week, 6 weeks E: 15 min, 3 times a week, 6 weeks	Walking on a treadmill	Control training with motor imagery training of normal walking	FRT	+
E/C: 40 min, 5 times a week, 5 weeks	Classic rehabilitation management using the bobath method	Partial body-weight supported gait training with the gait trainer	BBS Step test	= § = §
E: 50 min, 3 times a week, 13 weeks C: 1 hour, 1-3 times a week, 13 weeks	Conventional PT spasticity exercises, balance training	Aerobic treadmill training at 60-80% HRR	BBS	+
E/C: 30 min, 3 times a week, 4 weeks	Conventional PT with added stretching exercises and exercises using traditional motor developmental theory	E1:treadmill training with optic flow E2: treadmill training	FRT	+
E/C: 3 hours on 10 consecutive days	Overground gait training combined with activities to improve balance, strength, range of motion and coordination	Body-weight supported treadmill training combined with activities to improve balance, strength, range of motion and coordination	BBS Single limb stance	= =

Supplementary Table II (S.TableII) Continued

Study	PEDro score	Sample Size (E/C)*, pre- and post intervention	Age mean ± SD (years)	Time since stroke mean ± SD	Study population
Gait training					
Page et al. (2008)[20]	4	7 (4/3), no attrition	E+C: 61.3±12.3	E+C: 44±24 mo	Community dwelling
Peurala et al. (2005)[21]	6	45 (15/15/15), no attrition	E1: 53.3±8.9 E2: 51.2±7.9 C: 52.3±6.8	E1: 2.6±2 y E2: 2.4±3 y C: 4.0±6 y	Inpatient rehabilitation
Wang et al (2015)[22]	6	51 (25/26), no attrition	E: 62.0±9.5 C: 65.4±10.6	E: 18 (range 12-32) mo C: 19 (range 9-32) mo	Community dwelling
Westlake et al. (2009)[23]	6	16 (8/8) no attrition	E: 58.6±16.9 C: 55.1±13.6	E: 44±27 mo C: 37±20 mo	Unknown
Wu et al. (2014)[24]	5	Pre: 30 (15/15) Post: 28 (14/14)	E: 53.6±8.9. C: 57.4±9.8	E: 7.3±6 y C: 7.1±6 y	Unknown
Yen et al. (2008)[25]	7	14 (7/7) no attrition	E: 57.3±16.4 C:56.1±12.7	E: 2.0±1 y C: 2.0±2 y	Unknown
Yang et al. (2011)[26]	4	14 (7/7)	E: 56.3±10.2 C: 65.7±5.9	E:17±9 mo C:16±10 mo	Institutionalized and community
Multi sensory training					
Bayouk et al. (2006)[27]	4	16 (8/8)	E: 68.4±7.1 C: 62.0±4.6	E: 7.1±13 y C: 5.7±7 y	Community dwelling
Bonan et al. (2004)[28]	7	20 (10/10), no attrition	E: 49.5±10ǁ C: 49±17ǁ	E: 21±25 mo C: 21±10 mo	Community dwelling
Brogardh et al. (2012)[29]	9	31 (16/15), no attrition	E: 61.3±8.5 C: 63.9±5.8	E: 37±32 mo C: 33±29 mo	Unknown
Cha et al. (2014)[30]	7	pre: 20 (10/10) post: unknown	E: 59.8±11.7 C: 63.0±14.1	E: 15±6mo C: 15±5 mo	Unknown

	Training duration	Control training	Experimental training	Balance Outcome	Between-group difference[†]
	E/C: 30 min, 3 times a week, 8 weeks	Home Exercise Program, active RoM of ankle, knee and hip	NuStep exercise, seated locomotor training	BBS	+[§]
	E/C: 20 min, 5 times a week, 3 weeks *Conventional PT:* E/C: 55 min, 5 times a week, 3 weeks	Walking overground	Body weight supported gait training by a electromechanical gait trainer with (E1) or without (E2) FES	CoP velocity in AP and ML direction, Dynamic balance time	= =
	E: at least 60-90 min, 2 times a week, 12 weeks	No intervention	Personalized caregiver-mediated, home based intervention aimed at improving body functions and structural components, activites and participation	BBS	+
	E/C: 30 min, 3 times a week, 4 weeks	Manual body-weight supported treadmill training	Lokomat training in robotic orthosis	BBS	=
	E/C: 45 min, 3 times a week, 6 weeks	Body weight supported treadmill training with controlled assistance load to the paretic leg	Body weight supported treadmill training with controlled resistance load to the paretic leg	BBS	=
	E/C: 50 min, 2-5 times a week, 4 weeks E: 30 min, 3 times a week, 4 weeks	General PT: stretching, strengthening, balance and overground walking	Control training with body-weight supported treadmill training	BBS	=
dwelling	E/C: 20 min, 3 times a week, 3 weeks	Level walking on a treadmill	Control training with interactive VR scenes,	CoP displacement	=
	E/C: 1 hour, 2 times a week, 8 weeks	Task-oriented exercise program: standing and walking exercises	Control training with altered proprioception and vision	CoP variability and total displacement	+
	E/C: 1 hour, 5 times a week, 4 weeks	Vision free rehabilitation spasticity inhibition, walking and cycling	Control training with diminished vision	SOT	=
	E/C: 12 min, 2 times a week, 6 weeks	Vibration training with negligible amplitude	Vibration training with conventional amplitude	BBS	=
	E/C: 30 min, 5 times a week, 6 weeks *Conventional PT*: 30 min, 5 times a week, 6 weeks	Intensive overground gait training and conventional PT	Control training with rhythmic auditory stimulation during gait training	BBS	+

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Supplementary Table II (S.TableII) Continued

Study	PEDro score	Sample Size (E/C)*, pre- and post intervention	Age mean ± SD (years)	Time since stroke mean ± SD	Study population
Multi sensory training					
Lau et al. (2012)[31]	8	82 (41/41) no attrition	E: 57.3±11.3 C: 57.4±11.1	E: 4.6±4 y C:5.3±4 y	Community dwelling
Marin et al.(2013)[32]	8	20 (11/9) no attrition	E:62.3±10.6 C:64.4±7.6	E:4.3 ±2 y C: 4.3 ± 3 y	Unknown
Tankisheva et al. (2014)[33]	7	pre: 15 (7/8) post: 13 (6/7)	E: 57.4±13 C: 65.3±3.7	E: 7.7±9 y C: 5.28±4 y	Unknown
High intensity, aerobic exercises					
Chu et al. (2004)[34]	6	pre: 13 (7/6) post: 12 (7/5)	E: 61.9±9.4 C: 63.4±8.4	E: 3.0±2 y C: 4.2±2 y	Community dwelling
Jin et al. (2012)[35]	4	133 (68/65)	E: 57±6 C: 56±7	E: 19±5 mo C: 18±5 mo	Inpatient rehabilitation
Pang et al. (2005)[36]	8	pre: 63 (32/31) post: 60 (30/30)	E: 65.8±9.1 C: 64.7±8.4	E: 5.2±5 y C: 5.1±4 y	Community dwelling
Quaney et al. (2009)[37]	6	pre: 40 (20/20) post: 38 (19/19)	E: 64.1±12.3 C: 59.0±14.7	E: 4.6±3 y C: 5.1±4 y	Unknown
Other					
Choi et al. (2015)[38]	7	37 (19/18), no attrition	E: 49.1±11.9 C: 49.3±8.3	E: 18±7 mo C: 18±5 mo	Inpatient rehabilitation
Immink et al (2014)[39]	6	pre:25 (12/13) post: 22 (11/11)	E: 56±13.6 C: 63±17.4	E: 82±78 mo C: 23±13 mo	Unknown
Pandian et al. (2014)[40]	9[§§]	39 (20/19), no attrition	E: 44.5±13.6 C: 40.2±15.0	E: 13±8 mo C: 13±7 mo	Outpatient rehabilitation

Training duration	Control training	Experimental training	Balance Outcome	Between-group difference†
E/C 9-15 min, 3 times a week, 8 weeks	Standing exercises	Standing exercises with whole body vibration	BBS	=
			COP velocity and excursions	=
E/C: 120-420 seconds, 1-2 times a week, 17 sessions.	4-7 sets of whole body vibration in different direction and frequency while standing with knees 30º flexed	Standing with knees 30º flexed	BBS	=
E: max. 30 minutes, 3 times a week, 6 weeks	No intervention	Standing exercises on an vertical vibration platform	SOT	=
E/C: 1 hour, 3 times a week, 8 weeks	Seated arm exercise program	Aerobic water-based leg exercise program, at 50 to 80% HRR	BBS	=
E/C: 40 min, 5 times a week, 8 weeks	Low intensity overground walking training	Aerobic cycling exercise training with lower limb weights building up to 50-70% HRR	BBS	=
E/C: 1 hour, 3 times a week, 19 weeks	Seated upper extremity program, increasing muscle strength, RoM and agility exercises	Fitness and mobility exercise program, at 40 to 80 %HRR	BBS	=
E/C: 45 min, 3 times a week, 8 weeks	Home stretching exercises	Aerobic, resistive cycling exercises at 70% max heart rate	BBS	=
E/C: 15 min, 3 times a week, 4 weeks	Gait training on a treadmill	Cognitive – motor dual task with a random auditory cue while walking on a treadmill	ML and AP sway eyes open	+
			ML and AP sway eyes closed	+/=††
E: 90 min, once a week, 10 weeks and daily 40 minutes home practice	No intervention	Yoga exercises to promote light intensity physical activity, sensory and movement related awareness, active and passive relaxation and positive mood.	BBS	=
E/C: 1 hour, 3 times a week, 8 weeks	Standard motor rehabilitation of the paretic upper and lower limb	Additional resistive exercises of the nonparetic side and bimanual activities	BBS FRT	+ =

Supplementary Table II (S.TableII) Continued

Study	PEDro score	Sample Size (E/C)*, pre- and post intervention	Age mean ± SD (years)	Time since stroke mean ± SD	Study population
Other					
Rydwik et al. (2006)[41]	5	pre: 18 (9/9) post: 17 (8/9)	E: 74.9±8.7 C: 75.3±4.9	E: 43±18 mo C: 55±20 mo	Institutionalized and community dwelling
Schmid et al. (2012)[42]	6	pre: 47 (37/10) post: 39 (29/10)	E: 63.9±8.7 C: 60.2±8.9	E: 55±43 mo C: 36±24 mo	Unknown
Zheng et al. (2012)[43]	8	92 (45/47)	E: 69.1±5.0 C: 68.6±4.6	E: 33±6 mo C: 30±7 mo	Inpatient rehabilitation

BBS: Berg Balance Scale, C: Control group, CoG: Center of Gravity, CoP: Center of Pressure, E: Experimental group, FM: Fugl-Meyer Stroke Assessment Instrument, FRT: Functional Reach Test, HE: Home Exercises, HRR: Heart Rate Reserve, LOS: limit of stability test, mo: months, OT: Occupational therapy, PT: Physical Therapy, RoM: Range of Motion, SD: standard deviation, SOT: Sensory Organisation Test, VR: Virtual reality, y: years.

* If "no attrition" is stated, there were no drop outs or data was analyzed based on the "intention to treat"-principle.

† Reported results are direct post-intervention effects. Only significant group differences or significant group x time interactions are reported. +: training effect in favor of the experimental group, =: no difference between groups.

‡ Significant group differences for "standing on sway referenced support surface with eyes closed" and the vestibular ratio. All other conditions and ratios did not show significant group differences.

§ Between group difference calculated using the stated within group differences and SD's.

|| Median age ± interquartile range.

\# Significant group differences for "head straight with eyes open while standing on a foam surface, eyes closed while standing on a solid surface with head turned 30 deg to the left, and eyes closed while standing on a solid surface with head turned up positions. All other conditions did not show significant group differences.

** Significant group differences for "absent vision, sway-referenced support" condition. All other conditions did not show significant group differences.

†† Significant group differences for reaction time and endpoint excursion in forward direction. All other conditions did not show significant group differences.

‡‡ Significant group differences only in ML direction, not in AP.

§§ PEDro score not available from PEDro database. PEDro score was determined by the reviewers.

Training duration	Control training	Experimental training	Balance Outcome	Between-group difference[†]
E: 30 min , 3 times a week, 6 weeks	No intervention	A device improving active and passive RoM in the ankle	Romberg, semi-tandem and tandem stance	=
E: 1 hour, 2 times a week, 8 weeks	No intervention	Seated, standing and lying yoga exercises	BBS	=
E/C: 40 minutes, 5 times a week, 8 weeks	Static and dynamic balance exercises	Control training combined with cognitive tasks resulting in dual tasks	Static balance test: sway	+
			Static balance test: COP area	+

Supplementary Table III (S.TableIII) Pre- and post-intervention scores on the Berg Balance Scale

Study	Pre Intervention group	Post Intervention group	Pre Control group	Post Control group
Balance and/or functional weight-shifting training				
Cho KH et al. (2012)[2]	39.1±5.7	43.1±4.8	41.1±4.0	43.9±4.1
Farqalit et al. (2013)[3]	33.9±6.2	49.2±4.4	29.3±8.6	42.6±7.3
Kim et al. (2009)[7]	44.4±6.0	51,2±4.0	46.7±3.8	48.3±4.2
Lee et al. (2014)[8]	45.8±5.6	49.9±6.0	40.7±5.7	42.4±6.3
Lee et al. (2012)[9]	39.8±8.7	45.7±7.8	40.6±6.8	41.7±6.9
Llorens et al. (2014)[10]	47.2±6.7	51.0±4.6	44.4±7.0	46.2±5.7
Marigold et al. (2005)[11*]	44.7±6.5	49.1±5.0	44.8±7.1	48.1±5.7
Noh et al. (2008)[12]	43.3±5.2	50.9±2.8	42.3±7.3	44.5±6.7
Gait training				
Chen et al. (2014)[13]	50.4±4.8	53.1±2.9	48.7±4.4	50.1±3.9
Cho et al. (2014)[14]	39.3±4.13	42.6±3.1	39.5±5.7	41.0±5.2
Globas et al. (2012)[17]	49.3±6.5	51.1±6.4	45.2±11.0	44.3±11.9
Middleton et al. (2014)[19†]	-	50.4±5.4	-	47.2±7.0
Page et al. (2008)[20]	38.0±0.9	42.0±1.2	40.0±1.1	39.0±1.3
Wang et al. (2015)[22]	32.1±10.0	36.6±6.7	31.9±13.0	31.1±12.1
Westlake et al. (2009)[23]	46.9±7.5	48.3±6.8	47.0±7.0	51.0±5.4
Wu et al. (2014)[24]	44.1±8.8	45.6±9.3	43.6±9.0	45.5±8.8
Yen et al. (2008)[25]	50.3±3.3	52.4±2.9	50.6±3.6	51.6±3.1

Supplementary Table III (S.TableIII) Continued

Study	Pre Intervention group	Post Intervention group	Pre Control group	Post Control group
		Multi sensory training		
Brogardh et al. (2012)[29]	50.0±2.8	52.1±2.0	52.6±1.6	52.3±2.3
Cha et al. (2014)[30]	43.5±8.2	48.6±7.7	41.9±6.9	43.6±7.0
Lau et al. (2012)[31]	50.5±8.1	52.0±6.8	51.1±5.2	52.3±5.0
Marin et al. (2013)[32]	48.5±5.4	50.8±3.2	44.0±11.4	46.8±10.5
		High intensity aerobic training		
Chu et al. (2004)[34]	51.6±4.7	52.0±3.3	49.8±3.9	52.2±3.6
Jin et al. (2012)[35]	47.9±3.1	48.6±2.9	47.7±3.7	48.3±3.9
Pang et al. (2005)[36]	47.6±6.7	49.6±4.4	47.3±6.1	49.2±5.8
Quaney et al. (2009)[37]	40.4±9.7	41.7±9.6	38.9±14.7	39.1±14.3
		Other		
Immink et al. (2014)[39]	41.3±11.7	46.3±9.1	41.9±6.7	43.8±6.3
Pandian et al. (2014)[40]	46.9±6.8	52.5±3.1	43.5±8.7	46.0±8.4
Schmid et al. (2012)[42]	41.3±11.7	46.3±9.1‡	41.9±6.7	43.8±6.3‡

Berg Balance Scale Scores pre and post intervention (group means ± SD).
No pre- and post intervention scores could be extracted from the study of Dias et al. (2007).
* Both the intervention and control group received balance and/or weight-shifting training
† No pre intervention scores available
‡ No immediate post intervention measurements, but 8 weeks after completion of the training.

4

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Chapter 5

Development and process evaluation of a 5-week exercise program to prevent falls in people after stroke (the FALLS program)

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Abstract

Falls are a common complication after stroke, with balance and gait deficits being the most import risk factors. Taking into account the specific needs and capacities of people with stroke, we developed the FALLS program (FALL prevention after Stroke), based on the "Nijmegen Falls Prevention Program" (a proven-effective 5-week exercise program designed for community-dwelling elderly people). The program was tested in twelve community-dwelling persons with stroke, and a process evaluation was conducted with patients, trainers, health care professionals and managers. The FALLS-program was considered suitable and feasible by people with stroke in the study and relevant health care professionals, and recommendations for implementation in clinical practice have been suggested.

Introduction

Approximately 610,000 people in the United States and 41,000 in the Netherlands sustain a first-ever stroke each year.[1, 2] Although (partial) functional recovery is seen in a majority of those who survive their stroke, disabling cognitive, sensory and motor deficits persist in many subjects. Due to these deficits, falls are a common complication after stroke. A recent review showed that at one year follow up, 43-70% of the stroke survivors have fallen once, with a fall incidence rate of 1.4-5.0 falls each person-year.[3] Furthermore it stated that community-dwelling stroke survivors report walking as the most important activity leading to falls and that balance and gait deficits are identified as the most important risk factors.[3]

Although numerous articles have reported on the epidemiology of falling and fall risk factors after stroke, few studies have addressed the prevention of falls in people with stroke. A recent review identified a total of 13 randomised controlled trials in which falls had been included as an outcome measure, but in the vast majority of these studies falls only constituted a secondary outcome.[4] Hence, the interventions were not designed with the primary aim to prevent falls and, in addition, most of the studies were not adequately powered to identify potential reductions in falls.

Given the central role of balance and gait deficits in the etiology of falls after stroke, exercise programs seem to be the most promising approach to prevent falls. It is known that task-specific exercise programs improve balance and gait abilities in people with stroke and there is some preliminary evidence that they can reduce the number of falls as well.[3] Marigold et al. demonstrated that an agility exercise program improved quiet-stance stability, responses to balance perturbations and walking under challenging circumstances.[5] The fall rate for the agility exercise group was 0.10 falls/month per person versus 0.26 falls/month per person for the group receiving stretching and weight-shifting exercises (sham intervention), but this difference was not significant due to the relatively small group sizes. However, for a subgroup of participants (75% of the total group) with an increased fall risk, i.e. those with a history of falls, the authors found a significantly lower proportion of fallers in the experimental group (53%) compared to the sham group (87%) at one-year follow-up. Another study of a small group of people with stroke (n=10) also yielded promising results of exercise with respect to falls prevention.[6]

In the general elderly population, there is overwhelming evidence for exercise programs to be the most effective single intervention to reduce falls. Specifically multi-modal programs including strength, balance, endurance and flexibility have shown to be effective.[7-10] One such exercise program is the 'Nijmegen Falls Prevention Program' (NFPP), which was found to reduce the number of falls by 46% and to improve balance confidence and walking skills.[11] This program consists of three elements: 1. negotiating obstacles based on obstacles mimicking hazards in daily life; 2. walking exercises simulating walking in crowded environments; 3. training of fall techniques, derived from martial arts. The program is designed to include the most challenging circumstances of daily life, with the highest fall risk. With the introduction of the practice of fall techniques, the program not only aimed at a reduction in the number of falls, but also at the prevention of fall-related injuries and at a decrease of fear of falling.[12] An adjusted version of the NFPP (designed for persons with osteoporosis) was demonstrated to reduce the number of falls by 39% in conjunction with improved balance confidence.[13] We expect that an adjusted version of the NFPP, that takes into account the specific needs and capacities of people with stroke, will also be effective in preventing falls in this population.

Thus, the first aim of the present study was to develop a stroke-specific version of the NFPP, named the 'FALL prevention after Stroke' (FALLS) program. The program was tested in two groups of six community-dwelling persons with stroke. As a second aim, we conducted a process evaluation in patients, trainers, health care professionals and managers to identify the suitability of the FALLS program for people with stroke and its feasibility in clinical practice.

Material and Methods

Intervention

The 'FALLS-program' is based on the NFPP, a proven-effective 5-week exercise program, designed for community-dwelling elderly people with a history of falling.[11] To adjust the NFPP to the specific needs and capacities of people with stroke, a project committee was formed. The committee consisted of three physiotherapists specialized in stroke rehabilitation and the two primary investigators (HvD, resident in rehabilitation medicine; VW, movement scientist and physiotherapist). Two members of the committee (WH and VW) were also involved in the development of the original NFPP. The members studied the NFPP training protocol in detail and proposed a number of adjustments, additions and deletions of exercises. These were discussed among the committee members during three sessions of two hours, after which consensus was reached on the final protocol. The committee met a fourth time after the first group had finished the training program to discuss suggested changes on the basis of the observations and experience of the trainers.

The size of the training groups was reduced from 10 to 6 persons, because people with stroke were expected to need more intensive guidance and supervision. The number of supervisors was set at 2-3 physiotherapists per group, depending on the specific exercises. The walking exercises were revised to match with the smaller group size. The duration of the sessions was extended from 1.5 to 2 hours, and the number of repetitions of exercises was reduced because of the slower walking and movement speed of people with stroke. In addition, the higher physical and mental fatigability of people with stroke was taken into account by introducing a resting break of approximately 15 minutes. Furthermore, the rate at which the exercises increase in complexity was reduced (and, as a consequence, the final level of complexity) because of the physical impairments and the reduced speed of learning after stroke. Finally, solutions were formulated for the difficulties participants might encounter in several exercises due to paresis of the upper extremity. No specific homework exercises were included in the program, but participants were encouraged to implement the skills and knowledge as acquired during the sessions in their daily life. It was evaluated at the beginning of each session whether the participants had been able to do so.

The final FALLS program consists of 10 sessions (two sessions per week) of 2 hours each. A detailed overview of its contents is presented in table 1. The first session of the week is dedicated to an obstacle course that challenges balance, gait and coordination (figure 1). The obstacles mimic ADL activities with a high fall risk, like walking over doorsteps, stepping stones or various kinds of ground surface. In addition, the obstacle course contains elements to practice reaching sideways while sitting or standing and standing up without using the hands. It emphasizes on dynamical balance training, but also contains training of strength (e.g. m. quadriceps while standing up without using the hands). To further simulate the complexity of daily life, these balance and gait tasks are executed simultaneously with additional cognitive or motor tasks (20 and 25% of the time, respectively) and under visual constraints, e.g. dimmed light (15% of the time).

While negotiating the obstacles, participants not only practice their balance and coordination, they also learn to recognize and cope with potentially hazardous situations. The second session comprises walking exercises (45 minutes) and the practice of fall techniques (60 minutes). The walking exercises mimic walking in a crowded environment, where adjustment in walking speed and direction are required and collisions with other people or objects may perturb one's balance. Because participants are physically active during the exercises, endurance is trained as well. The practice of fall techniques is based on martial arts techniques and include falling in forward, backward and lateral directions. The difficulty is gradually enhanced by increasing the height from which subjects fall (from sit to stance).[11] These techniques have previously been demonstrated to be safe, even for persons with osteoporosis.[13] Furthermore, they are trainable in older adults and reduce the impact forces on the hip during sideways falls (as measured in a movement laboratory), which may reduce the risk of hip fractures when applied in real-life falls. The participants also perceived less fear of falling post intervention.[13]

Participants

The final FALLS-program was tested on twelve community-dwelling persons with stroke (divided over two consecutive groups of 6 participants). All participants had sustained a stroke more than 6 months ago, thereby eliminating spontaneous recovery processes to interact with training effects. They had all received (and completed) inpatient

Table 1 Final content of the FALLS-program

Session		Content	Min
1	*Obstacle course*	Uneven pavement, slopes, balance beam, walking under clothing line, various ground surfaces with doorsteps, narrow passage, stepping over a bench, stepping stones, transfer from stance to kneeling position, reaching, rotating, slalom with stepping over obstacles in lateral direction, walking backwards, sitting down and standing up from a chair without arm use.	105
2a	*Fall techniques*	Trunk stability while sitting, falling sideways from a sitting position, safely standing up from ground.	60
2b	*Walking exercises*	Walking in a row: changing walking speed and direction; throwing and catching a ball while walking: changing direction and avoiding collision with other participants; balance exercise: standing in a circle while pulling an elastic rope and walking in different directions.	45
3	*Obstacle course*	Motor dual task: walking in pairs holding a stick; visual deprivation: walking with dimmed light; cognitive dual task: count 1 specific sound in a piece of music while walking over the obstacle course.	105
4a	*Fall techniques*	Trunk stability, falling sideways and backwards from a sitting position, rolling exercises to prepare for a forward fall.	60
4b	*Walking exercises*	Walking in a row or square: changing walking speed and direction and backward walking; walking in a crowd with a balloon balancing on the hand; walking in pairs with badminton rackets and balloons.	45
5	*Obstacle course*	Motor dual task: walking with a serving tray; cognitive dual task: listening to a story and counting words while walking over the obstacle course	105
6a	*Fall techniques*	Falling sideways and backwards from a sitting position, falling sideways and forwards from kneeling position.	60
6b	*Walking exercises*	Shuttle walk exercise: walking at gradually increasing speeds (1.5-6 km/h); Playing a balloon with a badminton racket and one leg trapped in a hoop. Ball tunnel: walking through hoops while other participants throw balls.	45
7	*Obstacle course*	Different arrangement of the obstacles and walking in two groups in opposite directions; motor dual tasks: walking with serving tray with cups, walking with umbrella and filled bag.	105
8a	*Fall techniques*	Falling forwards and sideways from a kneeling position, falling backwards from a standing position.	60
8b	*Walking exercises*	Turning hoops: working together in a group to keep hoops turning; hockey game.	45
9	*Obstacle course*	Motor dual task: walking with serving tray, walking with a hockey stick and ball; cognitive dual task: count one specific sound in a piece of music.	105
10a	*Fall techniques*	Falling forwards and sideways while standing beside a thick mattress and falling backwards from a standing position.	60
10b	*Evaluation*	Evaluation of the total program	45

Figure 1 Obstacle course.

rehabilitation within the past two years and had a Functional Ambulation Categories (FAC) score of 4 or more (the capacity to walk independently on even terrain). Exclusion criteria were other musculo-skeletal conditions that affect balance or gait abilities, conditions in which physical activity is contra-indicated, use of psychotropic drugs and severe cognitive/behavioral problems (mini mental state examination below 24).

The protocol was approved by the regional medical-ethical committee. All participants gave written informed consent.

Process evaluation

The process evaluation was conducted at the level of the participants, the trainers (who developed the program and trained the subjects), other health care professionals and the management. With regard to the participants, attendance rates were registered and participant satisfaction was assessed by means of group-wise discussions and an anonymous questionnaire to be filled in at home after completion of the program.

The trainers (the physiotherapists who trained the participants) discussed in depth their observations and comments immediately after each session. They also established whether the session had been delivered according to protocol and whether the intended goals had been reached. Points for improvement were noted and applied to the following lessons.

Health care professionals' opinion on the suitability and feasibility in clinical practice of the program was assessed by interviewing physiotherapists, rehabilitation physicians and team managers. Thirteen physiotherapists from the rehabilitation center (not involved in the training) filled in a questionnaire, after having seen a presentation of the contents of the FALLS program. Subsequently, the answers to the questions were further discussed among the group members. Two rehabilitation physicians who have specialized in the treatment of people with stroke at the same rehabilitation center were interviewed on these topics as well. A face-to-face structured interview was held with two team managers to identify organizational opportunities and barriers for implementation of the program in clinical practice.

Data analysis

Descriptive statistics were used to analyse quantitative data from the questionnaires (answers to 'yes/no' questions and to multiple choice questions). The answers to the 'open' questions were categorised and presented separately. The same procedure was followed for the qualitative data from the group discussions and the interviews.

Results

Participants

The characteristics of the participants are presented in table 2. The attendance rate to the training sessions was 97.5%. Only 2 subjects missed one or two sessions, because of hospital visits or vocational obligations. There were no drop outs and no adverse physical effects were reported.

Eleven participants returned the evaluation questionnaires. The results are presented in table 3. In general, participants were satisfied with the frequency of the training sessions (91%), the duration of the sessions (100%) and the time of the day at which the sessions were planned (3 p.m. to 5 p.m., 100%). The majority (73%) was satisfied with the duration of the program. Two people considered the program too short, whereas one person thought the program was too long. With respect to the contents of the program, the three elements were generally judged pleasant and instructive. In addition, the guidance was considered to be good for all elements. The time spent per element was also judged positively, although for the fall techniques and walking exercises three people reported that the time spent on this element could be shorter (20%) or longer (10%). In the group-wise discussions it was pointed out that the participants were interested in booster sessions (a short session a couple of months after the end of the intervention, repeating the most important elements, particularly of the fall techniques).

In general, the different elements of the obstacle course, walking exercises and fall techniques were considered feasible by the participants, which demonstrates that the exercises matched their level of physical abilities. The balance beam and the stepping stones (see table 1) were reported as the most difficult elements of the obstacle course,

Table 2 Characteristics of the twelve participants.

Participant Characteristics	Mean±SD
Age	60.5±3.1
Months post stroke	16.2±1.9
Gender (%)	
Male	7 (58)
Female	5 (42)
Type of stroke (%)	
Haemorrhage	4 (33)
Infarction	8 (67)
Side of lesion (%)	
Right	5 (42)
Left	7 (58)
Motricity Index Leg	77.2±16.1
Fugl Meyer lower extremity scores	74.3±18.1
Berg Balance Score	50.5±5.0
Trunk Impairment Score	17.8± 3.4

The means and standard deviations are given, as well as the frequencies and percentages (between brackets). Maximum scores are 100 for Motricity Index , 100% for Fugl Meyer lower extremity, 56 for Berg Balance Score and 23 for Trunk Impairment Scale.

Table 3 Participant satisfaction regarding the FALLS-program

Component	Pleasant* Yes (%)	Instructive* Yes (%)	Time Spent * Good (%)	Guidance* Good (%)
Obstacle Course	91	100	100	91
Fall Techniques	91	100	73	100
Walking Exercises	100	100	73	100

*Questions asked with answer possibilities: did you find the component pleasant? (yes/no); did you find the component informative? (yes/no); how do you judge the time spent on the component? (too little/good/too much); how do you judge the guidance of the trainers during this component? (too little/good/too much).

falling sideways towards the affected side for the fall techniques and increasing speed for the walking exercises. For the obstacle course, the slalom and slopes were considered relatively easy. All participants who walked with a cane, were able to eventually complete the program without it.

As a result of the program, participants reported to have extended their range of physical abilities. The majority of the participants (73%) had been able to implement the training advice and acquired skills while walking under challenging circumstances in daily life. Seventy three percent reported to feel less at risk of falling and to have lower fear of falling. Those persons who did not perceive these benefits were the ones without initial fear of falling and who did not consider themselves at high fall risk prior to the intervention. Furthermore, all participants would recommend the FALLS-program to other persons with stroke.

Trainers

In general, the elements of the original FALLS-program were considered to be feasible for the participants, however, some adaptations were made based on the trainers' evaluations. These were discussed and agreed upon during the meeting of the project committee after the first group of participants had been trained. On the obstacle course, observing other participants was instructive for healthy persons, but not for persons with stroke due to attentional deficits. As a compensation, a set of optional balance exercises was offered to participants who had to wait for a supervisor.

The most important changes in the walking exercises were based on the observed cognitive and attentional problems of the participants. Cognitive elements were added and the number of exercises was limited to a maximum of 3 per session. To adapt the training to the variable abilities of the participants, each exercise consisted of a basic element of which the intensity or complexity was gradually increased. The fall training was feasible in its original design, as the participants were capable of executing the exercises according to the protocol. Therefore, no substantial adaptations had to be made.

Health professionals

All 13 physiotherapists completed the questionnaires. They all considered the FALLS program to be a good addition to the existing treatment programs. The majority considered it feasible (85%) for implementation in routine clinical practice. They judged the content of the program well-adjusted to the target group and did not expect organisational problems. A rehabilitation center was identified as the most suitable setting for the program (93%), whereas 70% thought it would also fit in a primary care physiotherapy practice.

In general, the program was deemed most suitable for outpatients directly following discharge from in-patient rehabilitation, or in the chronic phase after stroke (85%). Forty six percent considered the program feasible for inpatients as well. They agreed on independent walking ability (FAC 4 or 5) to be the necessary entry level for the program. In addition, balance problems and/or fear of falling were considered the main inclusion criteria, whereas participants should not suffer from severe cognitive and/or behavioral

problems, which influence basic understanding and cooperation. All the therapists deemed themselves capable of delivering the training sessions, but prior to working as a trainer, they would like to receive education on the specific contents of the program.
The interviews with the rehabilitation physicians yielded similar results. They suggested that the program was suitable both for patients in the chronic phase of stroke and for patients who are recently discharged from inpatient rehabilitation. If the program would be implemented, it should be delivered by physiotherapists specialized in stroke treatment, if necessary, with the help of other disciplines. In addition, they also advised participants to be screened for cognitive and/or behavioral problems by a rehabilitation physician prior to entering the program, who should also determine whether additional support would be needed.

Management

The managers considered the FALLS program to be a good addition to the present rehabilitation program. They also indicated that it would fit within the reimbursement system for health care costs in the Netherlands, such that the costs for delivering the program would be sufficiently covered. Experience with comparable projects did not show large barriers for implementation, besides planning.

The program could probably be offered 3 to 4 times a year, depending on the number of persons eligible for participation. Trainers could be educated in the specific elements of the program and interns could learn from more experienced trainers.

Discussion

In the present paper we described the development and process evaluation of the FALLS-program, a 5-week exercise falls prevention program designed for persons with stroke. The NFPP was adjusted to meet the special needs and capacities of people with stroke. The program was offered to two groups of six participants.

From the results of the present study we can conclude that the FALLS program is safe and feasible for participants in the chronic phase of stroke. There were no adverse events and the duration and frequency of the program were considered appropriate by the participants. There was an excellent attendance rate, which is important given the progressive nature of the program. These results are comparable to the original NFPP and to an adjusted version for persons with osteoporosis.[11, 13] Although data on the effectiveness of the program are not yet available, the experiences of the participants are promising. Most of them reported that their fear of falling was reduced after the program and that they felt to have improved balance maintenance while walking under challenging circumstances. The original NFPP has already been proven to be effective in reducing the fall incidence after implementation in clinical practice.[14]

Although the effectiveness of the FALLS program still needs to be established in a randomised controlled trial, the results of the questionnaires and interviews with the health care professionals and managers indicate that there appear to be no major hurdles for eventual implementation of the program in clinical practice. The program should preferably be offered to outpatients, in the chronic phase after stroke or shortly after discharge from in-patient rehabilitation. It is known that fall incidence rates increase strongly in the first 8 weeks after discharge.[15] It is suggested that this increase is due to the fact that people with stroke are not optimally prepared for the challenges they have to face in daily life. Nevertheless, patients who have not followed the program after discharge from the rehabilitation center may still benefit from it in a later phase. These persons are likely to have experienced one or more falls and thus maybe feel a higher necessity to prevent falls. According to the health care professionals, the program should be embedded in specialized out-patient facilities of a rehabilitation center. In that case, trainers have elaborated experience with treatment of persons with stroke and there is a possibility of additional support from other disciplines (e.g. language and speech therapists or psychologist) for advice on guidance of participants with specific problems.

Furthermore, it was suggested that, to be included in the program, participants should be at increased fall risk: i.e. have balance and/or gait problems, fear of falling or a positive fall history. Participants should be independent walkers (FAC 4 or 5, with or without walking cane) and should not have severe cognitive, behavioral or language problems, which could interfere with basic understanding and cooperation. Screening by a rehabilitation physician prior to the program is therefore necessary.

A limitation of the present study is that it was conducted on a small group (N=12) of people with stroke. In addition, participants were mildly affected and had no or little cognitive problems. Therefore, the results can only be applied to this specific population. A second limitation is that the effectiveness of the FALLS program has not yet been established in a randomised controlled trial (with fall rate as the main outcome). Hence, the conclusions and recommendations regarding potential implementation of the program are somewhat premature.

Furthermore, although the management indicated that the costs of the program would be covered under the current reimbursement system in the Netherlands, the cost-effectiveness of the program should ultimately be demonstrated as well in order to support its implementation in the post-stroke rehabilitation program. At this moment, it is hard to estimate the potential cost-effectiveness due to the lack of information on the effectiveness of the program and on the average costs per fall in the population of people with stroke. The main costs for delivering the program would be the start-up costs (training of physiotherapists; ~2000 Euro material costs for the obstacle course and the walking exercises, assuming safety mats and regular physiotherapy equipment to be present) and personnel (~600 Euro per participant). If a reduction in fall rates could be achieved similar to the two prior studies on the Nijmegen Falls Prevention Program[11, 13], an average of more than one fall per participant could likely be prevented based on the previously reported fall rates of 1.4-5.0 falls per year in people with stroke.[3] In the general elderly population, the average costs per fall amount 1,059 to 10,913 US Dollar.[16] Hence, if the FALLS program would be effective in reducing the number of falls, these numbers indicate that it has good potential to be cost-effective as well.

In conclusion, with this process evaluation we have demonstrated that the FALLS program is perceived, both by the users and relevant health care professionals, to be safe and suitable for the specific group of people with stroke as included in this study. Implementation of the program within a specialized rehabilitation center is considered feasible by physical therapists, rehabilitation physicians and team managers, but this should be preceded by a large randomized controlled trial to establish the effects of the program on fall rates. The perceived improvements in balance control and confidence are promising and it is for future research to objectify these effects as well.

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Chapter 6

Does the FALL prevention after Stroke (FALLS) program improve balance and trunk control in the chronic phase? A pilot study

Submitted as
van Duijnhoven HJ, de Kam D, Geurts AC, Weerdesteyn V. Does the FALL prevention after Stroke (FALLS) program improve balance and trunk control in the chronic phase? A pilot study.

Abstract

Objective: To assess the mechanisms of potential beneficial effects of a fall-prevention exercise program for people after stroke (the FALLS program), in anticipation of a future randomized controlled trial. We hypothesized that the FALLS program would lead to improvements particularly in balance and trunk control tests.

Methods: Twelve persons in the chronic phase after stroke completed the 5-week, 10 sessions, FALLS program. Before and after the intervention, the following outcome measures were assessed: balance capacity (Berg Balance Scale, BBS); trunk control (Trunk Impairment Scale, TIS); comfortable walking speed (10-Meter Walking Test, 10MWT); functional mobility (Timed Up and Go, TUG); and falls efficacy (Falls Efficacy Scale, FES).

Results: After training, participants showed improved balance capacity (BBS group mean±SD: pre 50.5±5.0, post 52.6±3.3, p=0.049) and trunk control (TIS group mean±SD: pre 17.8±3.3, post 19.8±1.9, p=0.008). There were no significant differences for the other outcomes.

Conclusions: This study shows that both components of the FALLS program, namely dynamic balance and trunk control exercises, yield the expected gains in corresponding clinical test outcomes. The findings of the present study are promising for people in the chronic phase after stroke and warrant further investigation in a randomized controlled trial.

Introduction

Accidental falls are a common complication after stroke, even in the chronic phase (beyond 6 months post stroke). In this population, the fall rate is increased at least two fold compared to healthy controls.[1] These falls may come with serious consequences, as they involve an increased risk of osteoporotic fractures.[2] Balance and gait deficits have been identified as the most important risk factors for falls after stroke.[3] Several studies have therefore evaluated the efficacy of exercise training for preventing falls in people with stroke, but no significant reduction in fall rates could be demonstrated.[4] This is in contrast with the overwhelming evidence for the efficacy of fall-prevention exercise in community-dwelling elderly[5], which may be due to previous exercise programs not sufficiently targeting the key risk factors and circumstances of falls in the stroke population.[4]

Our group has previously designed and evaluated the Nijmegen Falls Prevention Program (NFPP) [6] and has demonstrated its efficacy in preventing falls in community-dwelling elders and older people with osteoporosis.[6, 7] Its content distinctly differs from other falls prevention exercise programs, which notion has recently attracted international attention.[8] Specifically, the NFPP incorporates 1) dynamic balance exercises that simulate fall-hazardous situations from daily life (e.g. stepping over doorsteps or walking on uneven surface), and 2) the practice of fall techniques, which also includes comprehensive preparatory trunk control training.[6, 8] We believe that this approach may also be advantageous for community ambulators in the chronic phase after stroke. The specific balance and gait exercises align very well with the reported circumstances of falls in this population[3], and its task-oriented approach is in agreement with current insights and recommendations on effective exercise therapy post stroke.[9, 10] Furthermore, the trunk control exercises included in the NFPP appear to be of particular relevance for people with stroke, as impaired trunk control is common post stroke and is known to be an important determinant of defective standing and walking balance.[11] Previous fall prevention programs in the stroke population have not specifically focused on these key ingredients (i.e. task-oriented dynamic balance training and trunk control exercises) of the FALLS program.[4]

In a previous paper on the design and process evaluation of the FALLS program (FALL prevention for people after Stroke program), we have reported the stroke-specific amendments to the NFPP that were deemed necessary for taking into account the specific needs and abilities of this population. Our process evaluation showed that this program was indeed safe and considered suitable for people after stroke.[12] In this phase I modelling study (according to the framework of Campbell et al[13]) in a convenience sample of 12 community-dwelling people in the chronic phase after stroke we also aimed to test whether both components of the FALLS program (i.e. dynamic balance and trunk control exercises) would yield the expected gains on the corresponding clinical test outcomes (i.e. Berg Balance Scale and Trunk Impairment Scale).

Methods

We recruited twelve persons in the chronic phase after stroke from our outpatient rehabilitation clinic. They had all sustained a stroke more than 6 months ago, had completed primary rehabilitation within the past two years, and had a functional ambulation categories (FAC) score 4 or 5. Exclusion criteria were other musculoskeletal conditions that affect balance or gait capacities, conditions in which physical activity is contraindicated, use of psychotropic drugs, and severe cognitive/behavioral problems (Mini-Mental State Examination < 24). All participants gave written informed consent and the study was approved by the regional medical ethics committee.

All participants completed the 5-week FALLS program (see for details on the content of the program our previous study[12]) and were assessed before and after 10 two-hour training sessions. The following outcome measures were assessed: balance capacity using the Berg Balance Scale (BBS); trunk control using the Trunk Impairment Scale (TIS); comfortable walking speed using the 10-Meter Walking Test (10MWT); functional mobility using the Timed Up and Go (TUG); and falls efficacy using the Falls Efficacy Scale (FES). Paired t-tests were used to compare pre- and post-intervention scores. The alpha level was set at 0.05.

Table 1 Characteristics of the participants (n=12).

Participants' characteristics	Mean±SD
Age	60.5±3.1
Months post stroke	16.2±1.9
Gender (%)	
Male	7 (58)
Female	5 (42)
Type of stroke (%)	
Haemorrhage	4 (33)
Infarction	8 (67)
Side of lesion (%)	
Right	5 (42)
Left	7 (58)
Motricity Index (leg)	77.2±16.1
Fugl Meyer Assessment (leg)	74.3±18.1

The means and standard deviations are given, as well as the frequencies and percentages (between brackets). Maximum scores are 100 for Motricity Index (leg) and 100% for Fugl Meyer Assessment (leg).

Results

For participants' characteristics see table 1. Balance capacity and trunk control significantly changed after training as demonstrated by an improvement on the TIS (Δ=2.0) and BBS (Δ=2.1), respectively (see table 2). There was a borderline significant increase in comfortable walking speed (Δ=0.24m/s). No significant changes were found for functional mobility or falls efficacy.

Table 2 Pre- and post-intervention scores of clinical tests.

Clinical test	Pre intervention	Post intervention	p-value
BBS	50.5±5.0	52.6±3.3	0.049
TIS	17.8±3.3	19.8±1.9	0.008
10MWT	3.40±0.84	3.64±0.92	0.066
TUG	11.99±3.14	11.34±2.69	0.167
FES	8.14±1.18	8.44±0.99	0.182

Mean scores of clinical tests before and after intervention (group means ± SD). TIS: Trunk Impairment Scale (range 0-23 points); BBS: Berg Balance Scale (range 0-56 points); 10MWT: walking speed on 10-Meter Walk Test (km/h); TUG: Timed Up and Go (s); FES: Falls Efficacy Scale (range 0-10 points).

Discussion

In this phase I modeling study[13], we assessed the mechanisms of action of the FALLS-program in community-dwelling people in the chronic phase after stroke. Following training, participants showed an improvement in balance capacity (BBS) and, more distinctly, in trunk control (TIS).

The observation that the FALLS program led to improvements in balance capacity is in line with the current notion that training in a task-specific and task-oriented manner is key to achieving functional gains.[9, 10, 14] By simulating fall-hazardous situations of daily life, the FALLS program capitalized on taking a task-specific and task-oriented approach for practicing balance control. Of note, this study demonstrates improvements in balance capacity in the chronic phase after stroke, which observation is in contrast to the general belief that functional recovery plateaus more than 6 months after stroke. In our recent systematic review and meta-analysis we presented evidence that balance capacity shows sensitivity towards task-specific training in the chronic phase after stroke[9] and the present results substantiate this notion.

Although the observed improvements in BBS scores are promising, the mean difference of 2.1 points is rather small. Yet, it has to be mentioned that the mean pre-intervention BBS scores of our participants (51 points) were not far from the maximum score (56 points), thus leaving limited room for improvement on this clinical outcome. As the BBS is known to have considerable ceiling effects[15], we recommend a more sensitive clinical test for assessing balance capacity (e.g. Mini-BESTest) in ambulatory people in the chronic phase after stroke being used in a future randomized clinical trial.

Another important finding of this study is that our participants also showed improvements in trunk control following completion of the FALLS program. This is in line with the few studies that have been published on trunk control training in the chronic phase post stroke, which have also reported training-induced improvements.[16, 17] As impaired trunk control is an important determinant of defective standing balance[11], the presently observed improvements in TIS scores may, therefore, have contributed to the gains in balance capacity. As such, we believe that trunk control represents a highly relevant, yet rather neglected target for training in the chronic phase after stroke.

The observed gains in TIS scores following the FALLS program can likely be attributed to the practice of fall techniques, which training component included preparatory seated and standing trunk control exercises and covered around a quarter of the total training time. Indeed, in a previous training study of our group that strictly focused on dynamic balance and step adaptations, TIS scores did not improve following a 10-session training program in a similar group of people in the chronic phase after stroke.[18] These observations suggest that task-specific training is also critical for improving trunk control.

This study shows the mechanisms of potential training effects of a short, intensive and task-oriented fall prevention program (the FALLS program) for community-dwelling people in the chronic phase after stroke. Although the number of participants included in this study did not allow us to evaluate whether the FALLS program reduced the number of falls in daily life, the previously established efficacy of the original NFPP in reducing fall rates in other fall–prone populations indicates its potential. Indeed, the observed improvements in balance capacity and trunk control may lower the risk of falling, given that balance impairments are a key fall risk factor after stroke.

Therefore, further investigation of the FALLS program in a randomized controlled trial is warranted. Its two key components (i.e. task-oriented dynamic balance training and trunk control exercises) yielded the expected gains in their corresponding test outcomes and should thus be retained in the final version of the program. Furthermore, a future randomized controlled trial should also include fall rates as a primary outcome.

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Chapter 7

Perturbation-based balance training to improve step quality in the chronic phase after stroke: a proof-of-concept study

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Abstract

Introduction: People with stroke often have impaired stepping responses following balance perturbations, which increases their risk of falling. Computer-controlled movable platforms are promising tools for delivering perturbation-based balance training under safe and standardized circumstances.

Purpose: This proof-of-concept study aimed to identify whether a 5-week perturbation-based balance training program on a movable platform improves reactive step quality in people with chronic stroke.

Materials and methods: Twenty people with chronic stroke received a 5-week perturbation-based balance training (10 sessions, 45 minutes) on a movable platform. As the primary outcome, backward and forward reactive step quality (i.e., leg angle at stepping-foot contact) was assessed with a lean-and-release (i.e., non-trained) task at pre intervention, immediately post intervention, and six weeks after intervention (follow-up). Additionally, reactive step quality was assessed on the movable platform in multiple directions, as well as the percentage side steps upon sideward perturbations. To ensure that changes in the primary outcome could not solely be attributed to learning effects on the task due to repeated testing, 10 randomly selected participants received an additional pre intervention assessment, six weeks prior to training. Clinical assesments included the 6-item Activity-specific Balance Confidence scale, Berg Balance Scale, Trunk Impairment Scale, 10-Meter Walking Test, and Timed Up&Go-test.

Results: After lean-and-release, we observed 4.3° and 2.8° greater leg angles at post compared to pre intervention in the backward and forward direction, respectively. Leg angles also significantly improved in all perturbation directions on the movable platform. In addition, participants took 39% more paretic and 46% more non-paretic side steps. These effects were retained at follow-up. Post intervention, Berg Balance Scale and Trunk Impairment Scale scores had improved. At follow-up, Trunk Impairment Scale and 6-item Activity-specific Balance Confidence scale scores had significantly improved compared to pre intervention. No significant changes were observed between the two pre-intervention assessments.

Conclusion: A 5-week perturbation-based balance training on a movable platform appears to improve reactive step quality in people with chronic stroke. Importantly, improvements were retained after six weeks. Further controlled studies in larger patient samples are needed to verify these results and to establish whether this translates to fewer falls in daily life.

Introduction

Falls are among the most common complications after stroke.[1] Post-stroke fall incidence rates vary between 1.4 and 5.0 falls each person-year.[2] Falls are associated with worsening of functional outcomes post stroke.[3] A vicious circle of falling, fear of falling and inactivity can lead to further functional decline.[2]

Impaired balance and gait capacities are the most important risk factors for falls after stroke.[4,5] Improving these capacities is, therefore, an important goal in rehabilitation. However, a Cochrane review on interventions for preventing falls after stroke did not show beneficial effects of exercise training aimed at improving balance and gait on fall rates.[6] This is in contrast with the overwhelming evidence from the healthy elderly population, in which group- and home-based exercise programs do reduce fall rates and fall risk.[7] The question arises whether the types of exercise training previously used in the stroke population are indeed suitable.

One important aspect that has yet received only limited attention in previous training programs for people with stroke is the role of reactive stepping responses while standing and walking.[8-10] Following balance perturbations, fast and accurate stepping is an essential strategy to prevent falling.[11, 12] People with stroke have an impaired capacity to execute such reactive stepping responses, particularly with the paretic leg.[13-18] In fact, impaired stepping responses have been related to falling in people after stroke[19] and have shown to be predictive of fall risk after discharge from inpatient rehabilitation.[20] Therefore, improving these reactive stepping responses following balance perturbations seems to be an important target for balance training after stroke.

Recent systematic literature reviews showed that perturbation-based balance training is effective to reduce fall risk in both healthy older adults and in people with Parkinson's disease.[21, 22] In addition, a prospective cohort study showed lower fall rates for a group of participants in the subacute phase after stroke who received perturbation-based balance training during inpatient rehabilitation, when compared to a matched historical control group.[8] Very recently, a first study on this type of training in the chronic phase after stroke has been published.[23] In this study, the experimental group received therapist-induced balance perturbations and demonstrated improved reactive balance control when tested under the trained circumstances. Yet, no significant reduction in fall rate was observed compared to the control group. These observations call for further research on the generalizability of perturbation-based balance training to non-trained circumstances in people with chronic stroke. In addition, it may be that the effects of perturbation-based balance training can be enhanced by further increasing the intensity and unpredictability of the perturbations, thus providing a greater challenge for this group.

For delivering challenging perturbation-based balance training under safe and standardized circumstances, computer-controlled movable platforms (e.g. the Radboud

Falls Simulator (RFS)[24]) are helpful. We here report the results of a proof-of-principle study to evaluate the effects of a 5-week training program on a movable platform, aimed at improving reactive step quality in multiple perturbation directions and at enhancing side stepping upon sideward perturbations with the paretic and non-paretic leg. As a primary outcome, reactive step quality in the backward and forward directions was assessed with a lean-and-release (i.e., non-trained) task at pre intervention, immediately post intervention, and at six weeks follow-up. In addition, reactive step quality was assessed on the movable platform in multiple directions, as well as the percentage side steps taken upon sideward perturbations. In the present study, we focused on community-dwelling people in the chronic phase after stroke, as in this phase no further neurological recovery should be expected.[25] In addition, during the chronic phase, people are frequently exposed to balance perturbations in daily life. We hypothesized that our participants would show improved reactive step quality and enhanced side stepping after completion of a 5-week perturbation-based balance training program.

Methods

Participants

From the outpatient rehabilitation population of our university hospital, a total of twenty persons in the chronic phase (>six months) after stroke were included. Participant characteristics are given in table 1. They had to be able to stand and walk 'independently' as defined by a Functional Ambulation Categories (FAC) score of 4 or 5.[26] Exclusion criteria were 1) other neurological or musculoskeletal conditions affecting balance; 2) health conditions in which physical exercise was contra-indicated; 3) use of psychotropic drugs or other medication negatively affecting balance; 4) severe cognitive problems (Mini Mental State Examination (MMSE) <24)[27]; 5) persistent unilateral spatial neglect (Behavioral Inattention Test - Star Cancellation Test <44)[28]; and 6) behavioral problems interfering with compliance to the study protocol. The study protocol was approved by the Medical Ethical Board of the region Arnhem-Nijmegen and all participants gave written informed consent in accordance with the Declaration of Helsinki. This study was registered in the Netherlands Trial Register (NTR number 3804, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3804).

Design and study protocol

We conducted a proof-of-principle study in which the participants received a 5-week perturbation-based balance training. Forty persons were invited for an intake visit to determine eligibility (figure 1), and (after inclusion, n=20) to determine participants' demographic and clinical characteristics (sex, age, months since stroke, type of stroke, affected body side, history of falls, quantitative vibration threshold (QVT)[29], Motricity

Table 1 Characteristics of study participants (n=20).

Sex (men/women, % men)	12/8, 60%
Age (years)*	60.1 (8.1)
Months since stroke*	50 (39.4)
Stroke type (ischemic/hemorrhagic, % ischemic)	12/8, 60%
Affected body side (left/right, % left)	12/8, 60%
Fall history (number of falls in previous year)*	1.6 (1.8)
MMSE (range: 0-30)*	27.8 (1.9)
QVT lateral malleolus affected side (range: 0-8)*	4.2 (2.2)
MI-LE (range: 0-100)*	63.3 (19.8)
FMA-LE (range: 0-100%)*	64.9 (17.7)
FAC (4/5, % FAC 4)	4/16, 20%

Abbreviations: MMSE: mini mental state examination; QVT: quantitative vibration threshold; MI-LE: Motricity Index lower extremity; FMA-LE: Fugl-Meyer assessment lower extremity; FAC: Functional Ambulation Categories. * Values are presented in means (SD).

Index lower extremity (MI-LE)[30], and Fugl-Meyer Assessment lower extremity (FMA-LE)[31]. In addition, at the intake visit, initial training intensity was determined on the platform for each participant in each perturbation direction (see *Intervention*). Thereafter, all assessments of reactive stepping as well as all clinical tests (see *Outcomes*) were performed by each participant at pre intervention, post intervention (6 weeks after pre intervention) and follow-up (12 weeks after pre intervention). Yet, 10 participants (50%) who were randomly selected based on block randomization with stratification for severity of paresis (Motricity Index – Leg < 64% vs. Motricity Index – Leg ≥ 64%), received an additional pre-intervention assessment of reactive stepping 6 weeks prior to the final pre-intervention assessment (see figure 1). By comparing the results of both pre-intervention assessments in this subgroup, we were able to account for potential effects of repeated testing on reactive stepping. In the week after the (final) pre intervention assessment, all participants started the 5-week perturbation-based balance training. More information about the study protocol as well as the raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher upon request.

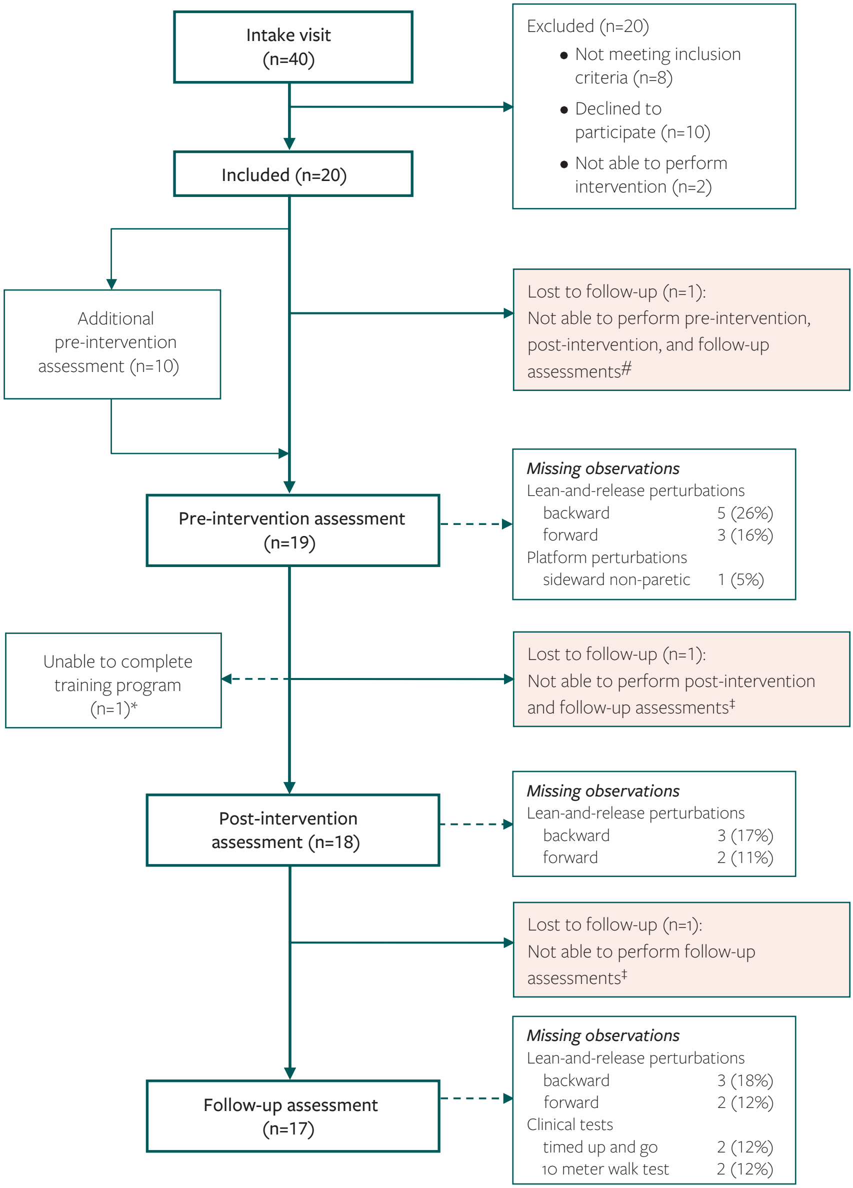


Figure 1 Flow of participants.

* One participant was able to complete only 3 out of 10 training sessions due to low back pain. Observations were included in all analyses according the to intention-to-treat principle.
# Lost to follow-up due to hip fracture after a fall, unrelated to the intervention.
‡ Lost to follow-up due to illness, unrelated to the study.

Intervention

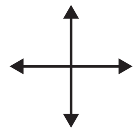
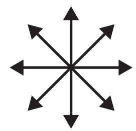
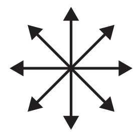
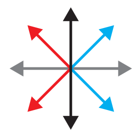
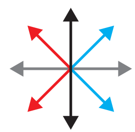
The 5-week perturbation-based balance training program was delivered on the RFS (120 × 180 cm; Baat Medical, Enschede, The Netherlands[24]). This movable platform can evoke reactive stepping responses by support-surface translations at magnitudes up to 4.5 m/s^2 in any given horizontal direction. In designing our new training program we aimed to achieve a high intensity (i.e., number of perturbations), large variation (i.e., directions of perturbations) and high challenge (i.e., high perturbation magnitudes) of reactive stepping exercises, yet under safe circumstances. The use of this computerized technology allowed us to set these perturbation parameters in a highly standardized manner.

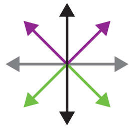
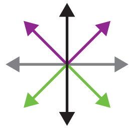
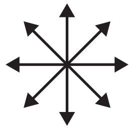
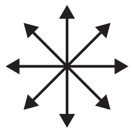
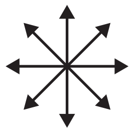
The selection of exercises in our program was inspired by the existing literature on reactive stepping responses in people with stroke and in healthy elderly.[32-35] After a balance perturbation, people with stroke show a low step quality in all directions, with a tendency to use multiple steps[33], a slow execution of steps[33], and a preference to use the non-paretic leg.[32, 34] Generally, the paretic leg shows difficulties both in executing a stepping response and in support limb control while stepping with the non-paretic side.[14] For sideward perturbations, side stepping has proven to be a more efficient and effective strategy than using cross-over steps[36, 37], yet people with stroke and healthy elderly tend to prefer cross-over steps during recovery responses from sideward perturbations.[36, 38] Therefore, the aim of the training program was to improve step quality after balance perturbations in eight different directions (forward, backward, both sideward, and four diagonal directions) by promoting the use of a single step, prevail side steps over cross-over steps, and enhance the speed of stepping. Reactive stepping was practiced both with the paretic and with the non-paretic leg. To achieve optimal results we used several previously reported and well known techniques like verbal feedback, blockage of the preferred leg, and stepping towards a target.[39]

Participants received 45 minutes of training, two times a week, 5 weeks in a row, under supervision of a trained physiotherapist. During each session, participants received a total of 60 to 80 perturbations. During all exercises, participants were secured by a safety harness attached to a sliding rail on the ceiling. The level of difficulty was gradually increased across sessions based on a standardized protocol, yet based on an individualized initial training intensity in each perturbation direction, as determined during the intake visit. Initial training intensity was defined as the maximal intensity at which participants were able to restore their balance without taking a step, plus 0.25 m/s^2. We progressed the difficulty of the training program by: 1) increasing the intensity of the perturbation; 2) increasing the unpredictability of the start and the direction of the perturbations across sessions; and 3) by adding dual tasks starting from training session six (see tables 2 and 3 for details on the content of the training program).

The 10 participants who performed two pre-intervention assessments were allowed to continue usual care during the 6 weeks in between these assessments, including any

Table 2 Content of the perturbation-based balance training program.

Session	Intensity of the perturbation	Predictability of the perturbation	Direction#	Additional training conditions
1	Initial*	Direction indicated and countdown to perturbation onset		
2	Initial	Direction indicated		
3	125% of initial	Direction indicated		
4	125% of initial	Random direction within blocks that contained perturbations in two directions [see graph: diagonal steps with paretic leg (blue) and non-paretic leg (red)]		
5	150% of initial	Random direction within blocks that contained perturbations in two directions [see graph: diagonal steps with paretic leg (blue) and non-paretic leg (red)]		

6	150% of initial	Random direction within blocks that contained perturbations in two directions [see graph: diagonal steps with either leg forward (purple) or backward (green)]		Cognitive dual task (visual Stroop task)
7	175% of initial	Random direction within blocks that contained perturbations in two directions [see graph: diagonal steps with either leg forward (purple) or backward (green)]		Motor dual task (marching in place)
8	175% of initial	All directions in random order		Cognitive dual task (visual Stroop task)
9	200% of initial	All directions in random order		Motor dual task (marching in place)
10	200% of initial	All directions in random order		Combined cognitive and motor dual task

* The initial training intensity was the maximal intensity at which participants restored their balance without taking a step, plus 0.25 m/s^2

The arrows in the graph depict the perturbation direction (forward, backward, paretic, non-paretic, and four diagonal directions).

Table 3 Training intensities per session (m/s²) (values are presented in means (SD)).

Session	Forward perturbations	Backward perturbations	Perturbations towards paretic side	Perturbations towards non-paretic side
1 and 2	1.02(0.21)	0.83(0.18)	1.06(0.22)	1.10(0.20)
3 and 4	1.28(0.24)	1.05(0.23)	1.35(0.28)	1.41(0.24)
5 and 6	1.53(0.30)	1.28(0.26)	1.61(0.31)	1.67(0.29)
7 and 8	1.80(0.34)	1.49(0.31)	1.88(0.39)	1.94(0.35)
9 and 10	2.04(0.41)	1.67(0.36)	2.14(0.44)	2.21(0.40)
Multiple stepping threshold	3.03(1.36)	2.21(0.88)	1.78(0.90)	1.68(0.96)

kind of physical therapy (if applicable). All participants were asked to refrain from additional balance exercises at home during the training period, but were free to receive (or continue) usual care during the follow-up.

Reactive stepping assessment

During pre, post, and follow-up assessments, reactive stepping was recorded following two types of balance perturbations: lean-and-release perturbations (backward and forward directions) and platform perturbations (backward, forward, sideward paretic, sideward non-paretic directions). During all recordings, participants wore their own shoes and stood at a fixed foot position with a distance of 4.5 cm between the medial sides of both feet. They wore a safety harness (attached to a sliding rail on the ceiling) to prevent them from falling, but which did not provide body (weight) support.

The lean-and-release task is a frequently used experimental paradigm for studying reactive stepping responses.[20, 32, 40] Importantly, this type of perturbation was not trained and was, therefore, selected as the primary outcome. Using different types of perturbation for training and assessment is in line with a previous study on perturbation-based balance training.[35] Participants were instructed to lean into the tether at an inclincation angle of 10° and, upon its unexpected release, to recover their balance by taking a single step. They were free to select which leg they used for stepping. After several practice trials, 10 outcome trials were recorded, five trials in the backward and five trials in the forward direction.

During the platform perturbation trials, participants received unpredictable and sudden horizontal translations in the forward, backward, sideward paretic, and sideward non-paretic directions. They were instructed to recover their balance with a single step. Perturbations consisted of an acceleration (300 ms), constant velocity (500 ms), and deceleration phase (300 ms). During the first assessment, the perturbation intensity was gradually increased with increments of 0.25 m/s^2 until the participants reached the maximum intensity at which they were able to recover their balance with one step (multiple stepping threshold, maximal 4.5 m/s^2). During the subsequent assessments, we used a fixed protocol with random perturbations in each direction, until the individual multiple stepping threshold (as determined during the first assessment) was reached. During all assessments, we ultimately recorded six outcome trials, three trials at the multiple stepping threshold and another three trials at one level (+0.125 m/s^2) above this intensity.

In addition to these formal assessments, we also monitored progress of participants' reactive step quality on the platform across training sessions (sessions 1, 4, 7, and 10). Due to time limitations or technical problems, we managed to do this in full for 14 of the 20 participants. These participants received additional platform perturbations after the training session, alternating in the forward and backward directions, at the maximum of their capacity (i.e., 0.125 m/s^2 above their individual multiple stepping threshold).

Reactive stepping responses were recorded at 100 Hz using an 8-camera 3D motion capture system (Vicon Motion Systems, Oxford, UK). Reflective markers were placed on anatomical landmarks according to the Vicon Plug-in-Gait model.[41] An additional reflective marker was placed on the translating platform to correct marker positions for platform movement. Marker trajectory data were filtered with a second order, 5 Hz low-pass, zero-lag Butterworth filter.

From these data, we assessed the quality of the reactive step. This step quality is typically determined by how far the stepping foot is placed away from the center of mass (CoM) into the direction of the induced loss of balance.[16, 42-45] We expressed this foot-to-CoM relationship as the leg angle at first stepping-foot contact (figure 2). In previous studies, the leg angle at stepping foot contact accurately distinguished between falls and successful recovery in healthy young subjects[44] and between single and multiple reactive steps in older women[43] and stroke survivors[18]. The leg angle was defined as the angle between the vertical and the line connecting the mid-pelvis to the 2nd metatarsal (backward and forward perturbations) or to the lateral malleolus (sideward perturbations) of the stepping foot. Larger positive leg angles correspond to better step quality.

Outcomes

The primary outcome was reactive step quality (i.e., leg angle at first stepping-foot contact) following lean-and-release perturbations in the backward and forward directions. The reactive step quality in four directions and the proportion of side steps upon sideward perturbations on the platform were used as secondary outcome measures. In addition, several clinical tests were performed, namely: 1) the 6-item short version of the Activity-specific Balance Confidence scale (6-ABC; range: 0-100%) to assess the balance confidence for performing daily-life activities[46]; 2) the Berg Balance Scale (BBS; range: 0-56) to test balance performance during activities of varying difficulty[47]; 3) the Trunk Impairment Scale (TIS; range: 0-23) to evaluate static and dynamic sitting balance and coordination of trunk movement[48]; 4) the 10-Meter Walking Test at comfortable walking speed (10-MWT); and 5) the Timed Up and Go test (TUG) to quantify functional mobility[49]. To determine the ability of participants to recover balance according to the instructions (i.e., with a single step), we also calculated the success rate for the lean-and-release and platform perturbations.

Statistical analysis

We first verified by means of Generalized Estimated Equations modeling (GEE, auto-regressive correlation structure) that potentially confounding variables (i.e., initial inclination angles for lean-and-release perturbations, the stepping leg (paretic/non-paretic), the maximal percentage of body weight supported by the harness system, and the angle of the trunk with the vertical at first stepping-foot contact) were not different between pre intervention, post intervention and follow-up for the primary outcome assessments. As these analyses yielded no significant effects of time, we did not include these variables in further analyses.

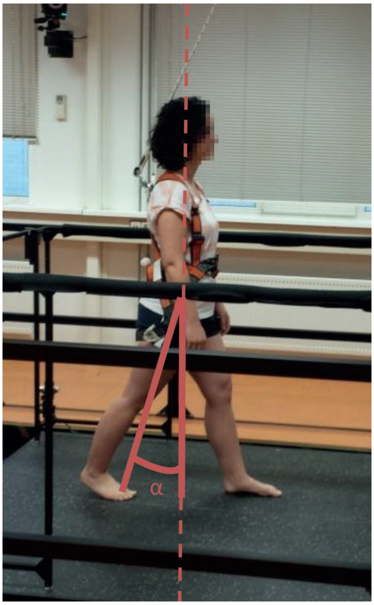


Figure 2 Definition of the leg angle.

Reactive step quality was expressed as the leg angle (α) at stepping-foot contact. This figure shows the leg angle for a backward step.

To study changes in the primary and secondary outcomes (i.e., leg angles, percentages side steps, clinical scales) following training, we conducted a GEE analysis with time (pre intervention, post intervention and follow-up) as within-subject factor. Furthermore, for the subgroup of participants who received two pre-intervention assessments, we determined the effects of repeated testing on reactive stepping by means of paired t-tests. Statistical analyses were performed with SPSS (version 22.0). $P<0.05$ was considered statistically significant.

Results

The inclusion flow diagram (figure 1) shows the numbers (and reasons) of participants who were lost to follow-up as well as any missing observations at the assessments. No intervention-related adverse events were reported. Table 4 shows a detailed overview of all outcome measures at pre intervention, post intervention and follow-up (n=20), together with the reactive stepping data for the two pre-intervention assessments (n=10). Participants were not always able to regain balance with a single step. Table 5 shows the percentage of successful lean-and-release and platform perturbation trials at pre intervention, post intervention and follow-up.

Lean-and-release perturbations

Backward and forward leg angles at post intervention were significantly larger compared to pre intervention (backward: $\Delta_{pre\text{-}post}$=4.3±1.3°, p=0.001; forward: $\Delta_{pre\text{-}post}$=2.8±0.7°, p<0.001; figure 3 and table 4). These larger leg angles were retained six weeks after training at follow-up (backward: $\Delta_{pre\text{-}fu}$=3.8±1.2°, p=0.001; forward: $\Delta_{pre\text{-}fu}$=2.7±0.6°, p<0.001). For both directions, leg angles were not different between the two pre-intervention assessments.

7

Platform perturbations

For backward and forward platform perturbations, leg angles at post intervention were significantly larger compared to pre intervention (backward: $\Delta_{pre\text{-}post}$=4.1±1.2°, p=0.001; forward: $\Delta_{pre\text{-}post}$=2.5±0.8°, p=0.001; table 4). This difference in leg angle was retained at follow-up (backward: $\Delta_{pre\text{-}fu}$=4.5±1.2°, p<0.001; forward: $\Delta_{pre\text{-}fu}$=2.2±0.6°, p<0.001). For sideward perturbations, the percentage of paretic and non-paretic side steps increased from pre to post intervention (paretic: $\Delta_{pre\text{-}post}$=39±12%, p=0.001, figure 4A; non-paretic: $\Delta_{pre\text{-}post}$=46±9%, p<0.001, figure 4B). This effect was also retained at follow-up (paretic: $\Delta_{pre\text{-}fu}$=38±11%, p=0.001; non-paretic: $\Delta_{pre\text{-}fu}$=43±9%, p<0.001). Furthermore, the number of participants who took at least one side step had increased after training. Before the start of the intervention, six and ten participants took one or more side steps with the paretic and non-paretic leg, respectively, which numbers increased to twelve and

Table 4 Primary and secondary outcome measures

	Pre-intervention Mean (SE) (n=20)	Post-intervention Mean (SE) (n=20)	Follow-up Mean (SE) (n=20)	Main effect of time (p-value) (n=20)	First pre-intervention Mean (SE) (n=10)	Final pre-intervention Mean (SE) (n=10)	Main effect of time (p-value) (n=10)
Primary outcomes							
Lean-and-release perturbations							
Backward leg angle (°)	0.3 (1.2)	4.6 (1.3)	4.0 (1.2)	0.001	-1.6 (1.7)	-0.8 (1.2)	0.589
Forward leg angle (°)	22.4 (0.8)	25.2 (0.5)	25.1 (0.7)	<0.001	23.0 (1.1)	23.0 (1.2)	0.987
Secondary outcomes							
Platform perturbations							
Backward leg angle (°)	-2.0 (1.4)	2.1 (1.1)	2.5 (0.8)	0.001	-3.5 (1.7)	-3.2 (1.5)	0.730
Forward leg angle (°)	21.1 (0.8)	23.6 (0.5)	23.3 (0.7)	0.001	20.1 (1.5)	20.4 (0.8)	0.699
Paretic side step (%)	19 (8)	59 (11)	58 (11)	0.001	29 (15)	30 (15)	0.907
Non-paretic side step (%)	37 (10)	84 (6)	80 (7)	<0.001	21 (14)	38 (16)	0.374
Paretic side step leg angle (°)*	17.6 (1.5)	19.8 (1.3)	19.4 (1.2)	0.012			
Non-paretic side step leg angle (°)*	17.6 (0.7)	18.8 (0.6)	19.7 (0.5)	0.001			
Clinical scales							
BBS	52.4 (0.9)	53.3 (0.7)	52.7 (0.8)	0.047			
TIS	16.1 (0.6)	17.9 (0.7)	16.7 (0.6)	<0.001			
6-ABC	41.5 (5.7)	45.1 (4.8)	49.4 (5.6)	0.014			
Comfortable walking speed (km/h)	3.5 (0.2)	3.7 (0.2)	3.6 (0.2)	0.127			
TUG (seconds)	10.4 (0.8)	10.8 (0.8)	10.0 (0.8)	0.307			

Estimated marginal means (standard errors) for leg angles, percentage side steps, and clinical scales at pre intervention, post intervention and follow-up for the total study sample (n=20) and mean values (standard errors) for leg angles and percentage side steps at the first and final pre-intervention assessment (n=10).
*Only three participants who received two pre-intervention assessments (n=10) took a paretic side step at both assessments, whereas none of the participants took a non-paretic side step at both assessments. Therefore, sideward leg angles were not compared between pre-intervention assessments. BBS: Berg Balance Scale (range: 0-56), TIS: Trunk Impairment Scale (range: 0-23), 6-ABC: 6-item short version of the Activity-specific Balance Confidence scale (range: 0-100%), TUG: Timed Up and Go test.

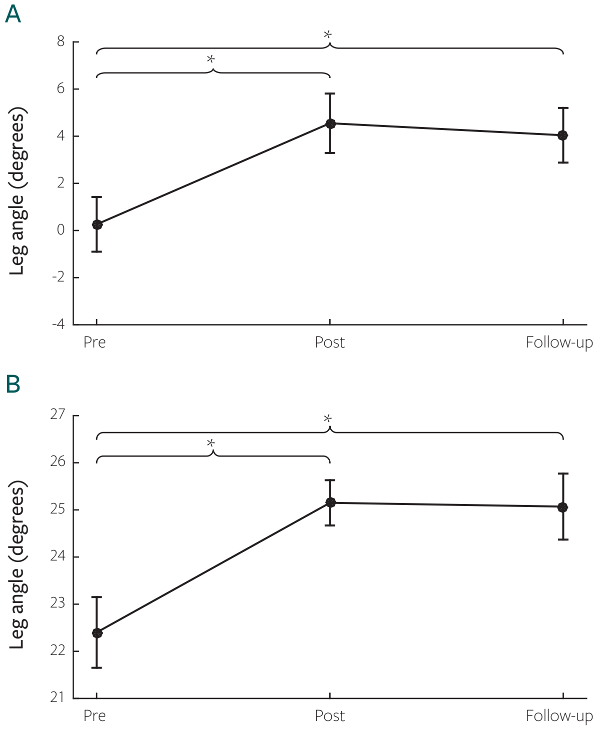


Figure 3 Lean-and-release perturbations

Step quality (i.e., leg angle) for lean-and-release perturbations in the backward (**A**) and forward (**B**) directions.

seventeen at the post- intervention assessment. For side steps towards the paretic side, leg angles increased from pre to post intervention ($\Delta_{pre\text{-}post}$=2.3±0.8°, p=0.004), which effect was retained at follow-up ($\Delta_{pre\text{-}fu}$=1.9±0.7°, p=0.006). For side steps towards the non-paretic side, leg angles at post intervention were not significantly larger compared to pre intervention, although a trend towards larger leg angles was visible ($\Delta_{pre\text{-}post}$=1.2±0.7°, p=0.075). Six weeks after training, at follow-up, non-paretic leg angles were significantly larger compared to pre intervention ($\Delta_{pre\text{-}fu}$=2.1±0.6°, p=0.001).

Clinical tests

Participants had a slightly higher BBS score at post compared to pre intervention ($\Delta_{pre\text{-}post}$=0.9±0.4, p=0.021), however, this effect was not retained at follow-up ($\Delta_{pre\text{-}fu}$=0.4±0.6, p=0.493). Yet, TIS scores at post intervention and at follow-up were significantly higher compared to pre intervention ($\Delta_{pre\text{-}post}$=1.8±0.5, p<0.001; $\Delta_{pre\text{-}fu}$=0.7±0.3, p=0.022). The difference in 6-ABC scores between pre and post

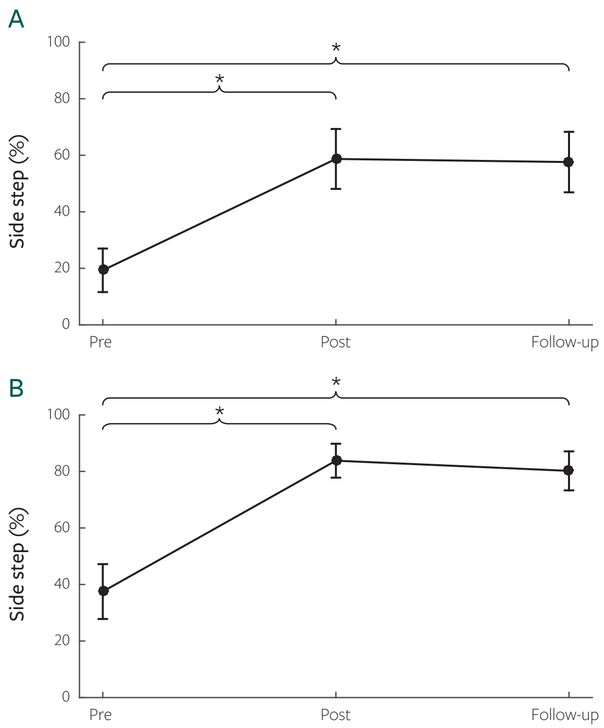


Figure 4 Sideward platform perturbations

Percentage of side steps for platform perturbations in the sideward paretic (**A**) and sideward non-paretic (**B**) directions.

Table 5 Percentage (SD) of trials recovered with a single step.

	Pre intervention	Post intervention	Follow-up
Lean-and-release perturbations			
Backward	64 (44)	73 (42)	80 (39)
Forward	73 (41)	82 (33)	81 (35)
Platform perturbations			
Backward	38 (24)	81 (23)	85 (25)
Forward	56 (35)	92 (18)	93 (14)
Towards paretic side*	28 (21)	66 (41)	69 (37)
Towards non-paretic side*	36 (32)	92 (12)	80 (25)

*N.B. This concerns both side steps and cross steps.

intervention did not reach statistical significance ($\Delta_{pre\text{-}post}$=3.7±3.1, p=0.240), however, at follow-up, participants rated their balance confidence significantly higher compared to pre intervention ($\Delta_{pre\text{-}fu}$=7.9±2.9, p=0.007). For comfortable walking speed and TUG no significant differences were found between pre intervention, post intervention, or follow-up.

Progress of step quality

During the intervention period, backward leg angles increased from training session 1 to 7 ($\Delta_{S1\text{-}S7}$=3.4±4.8°, p=0.041), but did not further increase at subsequent sessions. The forward leg angle increased from session 1 to 4 ($\Delta_{S1\text{-}S4}$=1.8±2.6°, p=0.033), but did not further increase at subsequent sessions (figure 5)

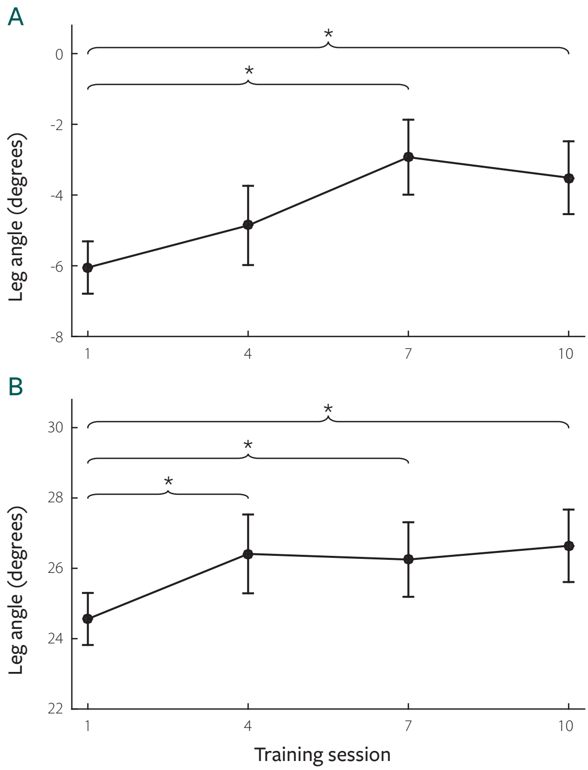


Figure 5 Course of leg angle improvement across training sessions.

Course of improvement in step quality (i.e., leg angle) across training sessions 1, 4, 7 and 10 for backward (**A**) and forward (**B**) platform perturbations. For practical reasons, we placed the reflective markers during the training sessions on the feet and L4 vertebra, instead of on the feet and both spina iliaca as was done during the formal assessments. Therefore, leg angles from the training sessions and assessments are not directly comparable. * p<0.05

7

Discussion

This proof-of-principle study investigated whether a 5-week perturbation-based multidirectional balance training program was able to improve reactive stepping in 20 persons in the chronic phase after stroke. In accordance with our hypotheses, we found that after completion of the training program reactive step quality had improved in the backward, forward, and both sideward directions. In addition, both paretic and non-paretic side steps were more frequently used for recovering balance upon sideward perturbations. Both types of effect were retained at follow-up. Several clinical scales showed significant immediate (BBS, TIS) and/or delayed (TIS, 6-ABC) training effects as well, albeit relatively small sized compared to the assessments of reactive stepping.

The hypothesis that our perturbation-based balance training would improve step quality in people with chronic stroke was corroborated by an increase in leg angle at first stepping-foot contact following lean-and-release perturbations of 4.3 (backward) and 2.8 degrees (forward) between pre and post intervention. This parameter has previously been shown to be a valid indicator of reactive step quality, as it accurately distinguished between successful (no fall) and unsuccessful (fall) recovery following large balance perturbations[44] and between single and multiple stepping in elderly individuals and people with stroke.[18, 43] At post intervention, the leg angles during the platform perturbations showed similar improvements as those observed during lean-and-release perturbations (4.1 and 2.5 degrees in the backward and forward directions, respectively). As the lean-and-release perturbations were not included in the training program, we conclude that generalization of the training effects to non-trained tasks has occurred, which implies 'real' training effects. Importantly, these improvements were retained for both types of perturbations after a period of 6 weeks during which no further practice of reactive stepping took place. Although these results are promising, it remains unknown for how long the observed improvements in reactive stepping are retained after this follow-up period of 6 weeks.

The notion that perturbation-based balance training can improve reactive stepping is in accordance with a previous study in community-dwelling older adults.[50] After 6 weeks (18 sessions of 30 minutes) of perturbation training, these elderly persons more frequently used single stepping responses and had less foot collisions during sideward perturbations. Since foot collisions mostly occur during cross-over steps, the reduction in collisions is in line with our observation of more side steps being taken after the training. Only one case study in a sub-acute stroke patient[51] has previously been published on training-induced improvements in reactive step quality. This study demonstrated increased effectiveness of reactive stepping responses and increased use of the paretic leg for stepping after targeted perturbation training. As the training was provided in the sub-acute phase, it remained unknown whether improved reactive stepping was caused by spontaneous neurological recovery, by training-induced functional recovery, or by a combination of both. Although, generally, neurological (motor) recovery cannot be expected beyond three months after stroke[52], functional recovery can still be reached in the chronic phase.[53] In this study, we indeed found that targeted balance training resulted in (further) functional recovery in a relatively high functioning group of chronic stroke patients. During training, participants were 'forced' to step with both the paretic and non-paretic leg in response to challenging perturbations. This type of training may unmask latent motor capacity, especially of the proximal leg and trunk muscles, that may have decayed as a result of stroke. This process may be based on the same mechanisms that underlie the effects of constrained induced movement therapy of the upper limb, but the exact neurophysiological mechanisms are a relevant topic for further research. As there are no established methods for measuring reactive step quality in people with stroke, the clinical relevance of the presently observed improvements remains to be identified. Nevertheless, in young adults an increase in leg angle of just 1 degree resulted in a threefold greater odds of successfully recovering from a large backward perturbation.[44] Hence, we conclude that the presently observed improvements in step quality are substantial, and most likely clinically relevant.

Although our training period of 5 weeks appears sufficiently long to achieve gains in reactive stepping, we raise the question whether there might have been further room for improvement. In the first training session, we conservatively chose a perturbation intensity only slightly above the individual stepping thresholds. Perturbation intensity was gradually increased each week according to a pre-defined protocol. Yet, it turned out that in the anteroposterior directions, the average perturbation intensities in the final training sessions were still below the participants' multiple stepping thresholds, as measured during the first balance assessment (see table 3). In addition, we monitored progress in forward and backward step quality (across sessions 1, 4, 7 and 10) and observed a plateau from session 4 onwards for forward and from session 7 onwards for backward step quality (see figure 5). These observations indicate that we have been rather conservative in progressing the level of difficulty across training sessions. Hence, for future application of the training protocol, we suggest to further challenge the participants by including greater increments in perturbation intensities.

The improvements that we observed in reactive stepping were accompanied by a perceived increase in balance confidence (as shown by the higher scores on the 6-ABC at follow-up). Yet, we found only minor and transient gains on the BBS as a clinical balance test, which were not considered clinically relevant. In the remaining clinical outcomes, we found no significant changes, except for a modest improvement in TIS scores at post intervention and follow-up. These observations are in line with a recent study on perturbation-based balance training in people in the sub-acute phase after stroke, which resulted in a reduction in fall risk and fall rates compared to a historical cohort, yet without between-group differences on clinical test outcomes.[8] One reason for this apparent discrepancy may be that the clinical tests included in our study do not capture (improvements in) reactive stepping, being the primary aim of our perturbation-based training program. Indeed, Innes et al[54] found a wide range in BBS scores across stroke participants, which did not correspond to their level of reactive stepping capacity. Another explanation may be that our participants already had near-maximum BBS scores (median: 54, range: 42-56) at pre intervention, leaving little room for further improvement. Yet, they did have impairments in reactive stepping, as their multiple stepping thresholds (i.e., the maximum perturbation intensity that could be sustained with a single step) were substantially lower than in healthy peers. For example, backward multiple stepping thresholds in our participants were 2.2 m/s^2 versus 3.5 m/s^2 in healthy peers.[38] Hence, it seems that for our group of community ambulators after stroke (comfortable walking speed >0.8 m/s in 16 of the 19 participants), the ceiling effect in BBS scores results in an underestimation of their balance impairments. Therefore, in future studies on perturbation-based training, we recommend to consider alternative clinical balance tests that do include an assessment of reactive balance control. The mini-BEST, for instance, includes reactive stepping tests and also has a smaller ceiling effect than the BBS [55], which may further add to its suitability for community ambulators.

In this study, the use of the RFS had the advantage of delivering a training program that was standardized, safe, challenging and of high intensity. Yet, it should be mentioned that this type of technology is not yet widely available and future developments should be targeted at designing cheaper and more easy-to-use training devices for perturbation-based balance training. Another limitation of our study is that the leg angle at first stepping-foot contact did not provide insight into which part of the stepping response specifically responded to the perturbation-based balance training. Such insight could further enhance our understanding of functional balance recovery after stroke and, thereby, help optimize rehabilitation strategies for this patient group. Although the fact that we did not include a control group is an obvious limitation, a subgroup of ten participants showed no differences in reactive stepping between the first and final pre-intervention assessments (before the start of the training). This result supports the notion that the observed improvements in reactive stepping after training are attributable to the perturbation-based balance training. Another limitation is the predictability of perturbation direction during the lean-and-release task. In the backward and forward platform perturbations, however, we found similar improvements in leg angles after training compared to the lean-and-release task. As perturbation direction during the platform perturbations was randomized across four different directions (backward, forward, sideward paretic, and sideward non-paretic), it appears that improvements in reactive stepping are not solely attributable to anticipation of participants.

Although we found improvements in reactive step quality after perturbation-based balance training, we did not evaluate whether our training program also contributed to fewer falls in daily life. Previous research showed, however, that impaired quality of reactive steps is related to increased fall rates during inpatient stroke rehabilitation[19], and that perturbation-based training in the sub-acute phase can reduce fall risk.[8] These findings suggest that perturbation-based balance training may be an effective intervention for reducing fall rates, not only in the sub-acute phase but also in the chronic phase after stroke.[9] Our chronic stroke participants were able to apply the learned stepping responses in non-trained circumstances and, importantly, retained their improvements in reactive stepping over a 6-week period without further practice. Therefore, perturbation-based balance training appears promising for improving the ability to recover from balance perturbations outside the laboratory or clinical setting (for example while experiencing trips or slips in daily life). Yet, further controlled studies in larger patient samples are needed to verify our results and to establish whether an improved step quality indeed translates to fewer falls in daily life.

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Chapter 8

Summary and general discussion

Summary

The aim of this thesis was to study the mechanisms underlying the problems people after unilateral supratentorial stroke experience during dynamic balance and gait tasks and to provide insight into the effects of dynamic balance and gait training in the chronic phase after stroke. In particular, I was interested in three important but relatively neglected components of dynamic balance and gait: trunk control, gait adaptability, and stepping reactions after balance perturbations. In this chapter I will summarize the findings of this thesis.

Part 1 Understanding dynamic balance and gait

In **chapter 2**, I studied the control of the relative movements of head, trunk and pelvis during lateral reaching in people early after stroke. This task is an example of proactive sitting balance, requiring good trunk control. Twenty-four persons within the first 12 weeks after stroke were compared to 20 healthy subjects. They all performed a standardized lateral reach task towards the non-paretic side. Using 3D motion analysis, movements of the head, trunk and pelvis were recorded. The movement sequence was calculated as well as angels at maximal reach and peak velocities of each body segment. We found that, when reaching sideways, people after stroke moved their pelvis first, followed by the trunk and head, whereas healthy subjects started with their head and then moved the trunk and pelvis. For all body segments, angles at maximal reach were significantly smaller for people after stroke when compared to healthy subjects. In addition, there were lower peak velocities during the reach (for head, trunk and pelvis) and return (for head and trunk). It was concluded that the movement pattern of head, trunk and pelvis in people early after stroke is altered when they reach sideways, and that they reach less far and move at a slower speed.

Chapter 3 addressed the underlying mechanisms of defective gait adaptability after stroke. I described a comparison of the motor responses of people in the chronic phase after stroke and healthy controls when performing an obstacle avoidance task. A total of 25 persons after stroke and 25 age-matched healthy subjects were included. All persons in the stroke group were more than 6 months post stroke onset and had a Functional Ambulation Categories score of 5. During treadmill walking, 30 obstacles were suddenly dropped in front of the paretic leg (or left leg of controls). Participants were instructed to avoid the obstacle by either lengthening or shortening the ongoing step. We determined the obstacle avoidance success rates. In addition, electromyography activity of bilateral biceps femoris, rectus femoris, tibialis anterior, and gastrocnemius medialis muscles was recorded as well as concomitant knee and hip angle courses and spatial characteristics of the avoiding step. People after stroke demonstrated markedly decreased obstacle avoidance success rates, most prominently under time pressure.

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They showed normal avoidance strategies, but had delayed and reduced electromyography responses, smaller joint angle deviations from unperturbed walking, and smaller horizontal margins from the foot to the obstacle. We concluded that even in persons who were mildly affected by stroke gait adaptability may be reduced, which may place them at risk of falling. Delayed and decreased muscle responses were identified as a possible mechanism leading to a diminished capacity to adapt step length when avoiding an unexpected obstacle.

Part 2 Training of dynamic balance and gait

To obtain insight into the effects of exercise training on balance capacity in people in the chronic phase after stroke, I performed a systematic review and meta-analysis, which is described in **chapter 4**. In this study we searched electronic databases for randomized controlled trials evaluating the effects of exercise therapy on balance capacity in the chronic phase after stroke. Studies were included if they were of moderate or high methodological quality (PEDro score ≥4). Data were pooled if a specific outcome measure was reported in at least 3 trials. To identify which training regimen was most effective, we performed a sensitivity analysis and consequent subgroup analyses for the different types of experimental training (balance and/or weight-shifting training, gait training, multisensory training, high-intensity aerobic exercise training, and other training programs). Forty-three randomized controlled trials out of 369 unique hits were included. A meta-analysis could be conducted for the Berg Balance Scale, Functional Reach Test, Sensory Organization Test, and mean postural sway velocity. A significant overall difference in favour of the intervention group was found for the Berg Balance Scale, Functional Reach Test, and Sensory Organization Test. Subgroup analyses of the studies that included Berg Balance Scale outcomes demonstrated a significant improvement after balance and/or weight-shifting training and after gait training, whereas no significant effects were found for other training regimens. We concluded that balance capacities can be improved by well-targeted exercise therapy programs in the chronic phase after stroke. Specifically, balance and/or weight-shifting and gait training were identified as successful training regimens.

In **chapter 5**, I addressed the development and process evaluation of a stroke-specific fall prevention program in people in the chronic phase after stroke (the FALL prevention after Stroke (FALLS) program). Taking into account the specific needs and capacities of people with stroke, we based this program on the "Nijmegen falls prevention program", a proven-effective 5-week exercise program designed for community-dwelling elderly people. The FALLS program was tested in 12 community-dwelling persons with stroke and a process evaluation was conducted with patients, trainers, health care professionals, and managers. People after stroke and relevant health care professionals deemed the FALLS program suitable and feasible.

Subsequently, in **chapter 6,** I described a phase 1 modelling study, assessing the effects of the FALLS program on a set of commonly used clinical tests. I hypothesized that this program would lead to improvements particularly in balance and trunk control tests. Twelve persons in the chronic phase after stroke completed the training for 5 weeks, with a total of 10 sessions. Before and after the intervention, we assessed the following outcome measures: balance capacity (Berg Balance Scale, BBS); trunk control (Trunk Impairment Scale, TIS); comfortable walking speed (10-Meter Walking Test, 10MWT); functional mobility (Timed Up and Go, TUG); and falls efficacy (Falls Efficacy Scale, FES). After the training, participants showed improved balance capacity and trunk control. There were no significant differences for the other outcomes. We concluded that this study provides preliminary evidence for the possible effectiveness of the FALLS program on balance capacity and trunk control. The findings of the present study are promising for people in the chronic phase after stroke and warrant further investigation in a randomized controlled trial, including fall rates as a primary outcome.

Chapter 7 showed the results of a 'proof-of-concept' study to identify whether a 5-week perturbation-based balance training program on a moveable platform would improve reactive step quality in people with stroke. Twenty persons in the chronic phase after stroke received a 5-week perturbation-based balance training program (10 sessions, 45 minutes). At pre-intervention, immediately post-intervention and six weeks after the intervention (follow-up), reactive step quality (i.e. leg angle at stepping-foot contact) was assessed following lean-and-release perturbations in the forward and backward direction (e.g. non-trained) and following perturbations on the moveable platform in multiple directions. In addition, we assessed the percentages of side steps after sideward perturbations on the platform. Finally, we performed clinical assessments, including the 6-item Activity-specific Balance Confidence scale (6-ABC), Berg Balance Scale, Trunk Impairment Scale, 10-Meter Walking Test, and the Timed Up&Go-test. To ensure that changes in the primary outcome could not solely be attributed to learning effects on the task due to repeated testing, 10 randomly selected participants received an additional pre-intervention assessment, six weeks prior to the start of the training. After training, we observed 4.3° and 2.8° greater leg angles following lean-and-release perturbations in the backward and forward direction, respectively, when compared to pre-intervention. Leg angles also significantly improved in all perturbation directions on the movable platform. In addition, participants took 39% more paretic and 46% more non-paretic side steps. These effects were retained at follow-up. At post intervention, BBS and TIS scores had improved. At follow-up, TIS and 6-ABC scores had significantly improved compared to pre-intervention. No significant changes were observed between the two pre-intervention assessments (n=10). It was concluded that a 5-week perturbation-based balance training on a moveable platform appears to improve reactive step quality in people with chronic stroke. Importantly, improvements were retained after six weeks. Yet, further controlled studies in larger patient samples are needed to verify these results and to establish whether the observed effects translate to fewer falls in daily life.

General discussion

Here, I will discuss the findings of this thesis. First, I will focus on the added value of assessing movement quality by manipulating dynamic task complexity and using instrumented assessments to better understand the underlying mechanisms of defective balance and gait. Thereafter, I will propose a theoretical framework on the complex interaction between dynamic balance and gait after (unilateral supratentorial) stroke and discuss the trainability of the most important elements within this framework. Finally, I will give recommendations for future rehabilitation and research.

Added value of task complexity and instrumented assessments for understanding dynamic balance and gait

In part 1 of this thesis I examined two important but relatively neglected components of dynamic balance and gait, namely trunk control and gait adaptability. Using 3D motion analysis and electromyography (EMG), we recorded two dynamic and challenging tasks (lateral reach and obstacle avoidance), revealing differences in the quality of movement between people after stroke and healthy controls. How should we interpret these differences?

When studying task performance after stroke in the clinic, we generally use observational tests. Such clinical tests typically describe whether a task can be completed successfully and/or capture speed or distance of the movement. In this thesis we found differences in clinical outcomes when people after stroke were compared to healthy controls. For instance, on the lateral reach task (chapter 2), people after stroke reached less far and at a slower speed; and when negotiating an obstacle during gait (chapter 3), patients showed diminished horizontal margins from the foot to the obstacle. The question arises whether such observable abnormalities are a direct result of damage to the sensorimotor system or perhaps due to compensatory strategies to remain stable and safe? To address this question, we need to compare the *complexity* of both tasks. The lateral reach task involved a simple instruction: "reach to the side with the unaffected arm as far as possible". No constraints on reaching distance or speed of reaching were imposed. Participants were able to choose any strategy to safely execute the task knowing that, with further and faster reaching, the risk of imbalance, and eventually a fall, would increase.[1, 2] As faster reaching diminishes the accuracy of the reach, the brain tends to slow down the movement to increase the probability of executing the task successfully (a phenomenon referred to as "speed-accuracy trade off").[3] It is therefore likely that the slower speed of reaching and the lower distance reached are due to compensatory strategies to preserve trunk control and postural stability. In contrast, the obstacle avoidance task was much more complex and imposed a considerable amount of time constraint. Participants were walking on a treadmill and were instructed to avoid obstacles that were unexpectedly dropped in front of the paretic leg at various instants of the gait cycle. Adding this type of time constraint imposed high demands on the capacity to quickly adapt gait and hampered the use of compensation strategies. Slowing down gait was impossible as the speed of the treadmill was fixed. Generally, the use of task and time constraints clearly hampers motor performance. Indeed, when people after stroke were asked to negotiate obstacles during over ground walking, considerably lower failure rates were reported when compared to the experimental setup used in chapter 3 (3% vs 70% errors, respectively).[4] Therefore, the observed errors on the obstacle avoidance task and the smaller horizontal margins from the foot to the obstacle seem to be the direct result of the brain damage rather than a reflection of compensatory movement strategies. Without increasing the gait complexity, these primary deficits would have remained unnoticed.

By means of 3D motion analysis and EMG recordings of the obstacle avoidance trials, we found delayed and reduced leg muscle responses leading to smaller joint angle deviations from unperturbed walking and smaller horizontal margins from the foot to the obstacle. Consequently, we observed higher failure rates compared to healthy subjects. These failures are probably (at least partly) related to the assessed leg motor impairments on the affected body side, but may also be due to impaired balance control. Presumably, impaired balance has an additional negative effect on obstacle avoidance capacity, as previously shown by a study on online step adjustments after stroke.[5] In that study, subjects were asked to step towards a target while standing with and without balance support. People after stroke showed large foot placement errors but, when balance was externally supported, they were able to decrease the foot placement errors considerably. Importantly, *instrumented assessments* of complex dynamic balance and gait tasks may reveal underlying deficits in the quality of movement execution that remain unrecognized when only speed or distance of movement are assessed. Analysis of these deficits provides insight in the mechanisms of altered task performance and can help to discriminate between primary deficits and compensatory phenomena. This discrimination is needed to target the right goals during balance and gait rehabilitation after stroke.

The use of instrumented measures also supported the interpretation of the impaired task performance during the lateral reach task. To date, trunk control after stroke under static and dynamic conditions has mainly been studied by using clinical or posturographic outcome measures.[6-9] These studies have shown that controlling the trunk may be challenging for patients with stroke and that sway control and weight shifting capacity while sitting differed from healthy controls, particularly in the first weeks after stroke onset. By means of 3D motion analysis we were able to show that, during a dynamic lateral reach task, people after stroke moved their body segments also in a different sequence compared to healthy controls. When asked to reach towards the non-paretic side, they started the movement with the pelvis and kept the trunk and head aligned in their initial orientation. As such, they seemed to move 'en bloc', initiating the movement bottom-up. In contrast, healthy controls showed a top-down pattern, starting with the head, followed by the trunk and pelvis. The abnormal 'en bloc' movement after stroke may be due to loss of motor selectivity of trunk muscles, comparable to the loss of motor selectivity (leading to abnormal and rigid muscle synergies) in the affected upper and/or lower extremity[10, 11], even though trunk muscle paresis may not be that apparent. An altered movement pattern as a result of trunk coordination deficits after stroke has been reported previously for other types of balance tasks, like turning when standing.[12-14] It is also in line with a study on a complex reach task, requiring adjustments of the reaching movements, which revealed subtle trunk control problems in the chronic phase after stroke.[15] Due to trunk coordination problems, people after stroke have less flexibility to maintain balance and ambulate, particularly when they need to respond to perturbations. Thus, even during relatively simple tasks, instrumented measures have an added value to understand the underlying mechanism of postural instability.

Overall, the subjects included in both observational studies were relatively mildly affected by stroke. In the lateral reach study, participants had a mean Rivermead Motor Assessment leg and trunk section score 8 out of 10, a Motricity Index – leg of 80% and a Trunk Control Test score of 92%. Participants in the obstacle avoidance study had a median Motricity Index - leg of 64%, a median Fugl-Meyer Assessment - leg of 68%, and a median Berg Balance Scale score 53 out of 56. Despite their relatively good motor recovery, participants still performed substantially worse on both motor tasks compared to healthy controls. It is likely that these differences in motor performance were provoked by adding a dynamic component to both the sitting and walking tasks, increasing their complexity, and could only be identified by using instrumented assessments of the quality of movement.

A framework on the complex interaction between dynamic balance and gait after stroke

This thesis provides insight into the mechanisms underlying deficits in dynamic balance and gait after stroke. In addition, it examines the possible effects of reactive balance control training. Before discussing the implications for rehabilitation and future research, I propose a theoretical framework on the complex interaction between dynamic balance and gait after stroke (figure 1). This theoretical framework is based on a previously drafted model of neural control of functional walking, describing three primary requirements for optimal gait capacity: equilibrium, stepping, and adaptability.[16] I adjusted these terms to three critical elements of efficient and safe community walking, namely *gait independence, gait pattern, and gait adaptability*. Furthermore, I added *balance control* (divided into steady state, proactive, and reactive balance control) and *leg motor control of the paretic leg*, which types of motor control underlie these critical elements of gait.

Gait independence refers to the capacity to walk alone or with a walking aid, but without assistance from another person.[17] It is the basic skill of moving forward in an erect posture without falling. The overall probability of initially non-ambulatory patients to regain gait independence after stroke is 60-65%.[17] Steady state balance control has been shown to be the most important determinant of regaining gait independence.[18, 19] In fact, recovery of standing balance after stroke intimately coincides with increasing gait independence.[20] Trunk control is the most important prerequisite for standing balance control, as the degree of trunk control correlates strongly with measures of (standing) balance[21] and the recovery of gait.[18, 19, 22] Notably, gait independence does not require refined motor control of both legs, which is inherent in the finding that stroke severity does not predict recovery of walking capacity.[20] This lack of association between paretic leg motor control and gait independence is coherent with the notion that many people with a lower limb amputation are perfectly able to reach gait independence with a lower-limb prosthesis, even though the prosthetic leg only provides passive mechanisms of support and motion. Indeed, after stroke, steady state standing balance can to a large extent be regulated by the trunk and the non-paretic leg.[23]

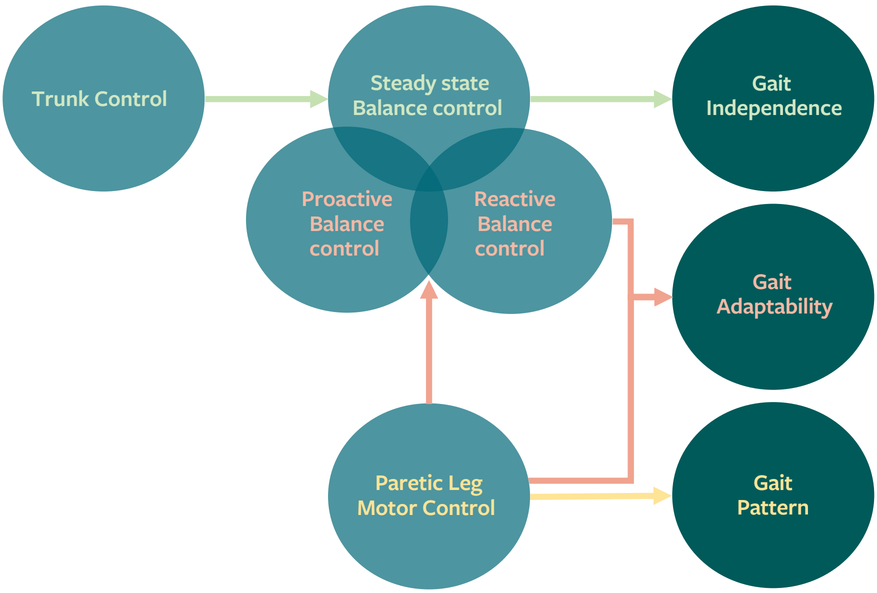

Fig 1 Theoretical framework on dynamic balance and gait after stroke

Once independence of gait is reached, the *gait pattern* becomes more important for efficient walking in daily life. The gait pattern is a sequence of repetitive movements of both legs in interaction with the trunk and the arms. After stroke, the gait pattern may be seriously affected primarily by impaired leg motor control on one side of the body as a result of the unilateral upper motor neuron lesion.[24, 25] Typically, people after stroke show greater involvement of the distal than the proximal leg muscles and greater strength, but also higher muscle tone and reflexes, in the leg extensors than the leg flexors.[24, 26] This so-called 'spastic hemiparesis' leads to an asymmetrical gait pattern, dependent on the location and severity of stroke and degree of sensorimotor recovery.[26] Besides its influence on the gait pattern, impaired leg motor control on the affected body side may also affect dynamic aspects of standing balance, such as pro- and reactive stepping upon (un)expected perturbations.[27]

Gait adaptability refers to the complex interaction between pro- and reactive balance control and leg motor control. It is defined as the capacity to adapt one's gait to comply with behavioural goals and meet the demands imposed by the environment.[16] Steady state walking already requires substantial balance control and (at least sufficient unilateral) leg motor control to keep the moving center of mass within the boundaries of the continuously changing base of support.[28] Steady state walking is already a pro-active task requiring constant feedforward control to navigate and anticipate possible obstacles on the road ahead. During more complex tasks (e.g. bending, turning, jumping) and in complex environments (e.g. slippery floor, obstacles, crowd), the demands imposed on the sensorimotor system further increase, requiring sufficient control of both legs in order to be able to make pro- and reactive stepping responses during walking. This high level of motor control typically involves contributions from multiple cortical areas, which is why gait adaptability is challenging specifically for people after stroke.[16] Indeed, as previously shown in some studies (including chapter 3 of this thesis), people after stroke show great difficulties with obstacle crossing and online stepping adjustments due to impairments in dynamic balance control and in selective motor control of the paretic leg.[5, 29-31]

Trainability of dynamic balance and gait after stroke

The above described theoretical framework on dynamic balance and gait after stroke (figure 1) can be used to better understand the effects of training, as described in this thesis and in the literature. However, before discussing the implications for balance and gait rehabilitation, it is important to address the (putative) mechanisms underlying functional recovery after stroke. The term functional recovery here refers to the capacity to use the trunk and upper and lower limbs in meaningful daily life tasks. Recovery of this capacity may be the result of either recovery of sensorimotor functions (e.g., muscle strength, motor selectivity, sensibility; so called 'restitution of function') or the learning of new sensorimotor strategies to accomplish the task in an adjusted manner (so called 'substitution of function' or 'behavioral compensation'). The latter form of functional recovery is often characterized by loss of movement quality (i.e., fluency, accuracy, speed). After unilateral supratentorial stroke, functional recovery is apparent to a substantial degree in almost all stroke survivors.[32] The proportional recovery of underlying sensorimotor functions follows a similar pattern in the majority of stroke patients for both the upper and lower extremity.[33, 34] Roughly, 70% of the stroke survivors show 70% restitution of their lost functions, a phenomenon known as the "proportional recovery rule". The remainder of the patients show less recovery or no restitution of function at all. It is, therefore, most likely that the restoration of sensorimotor functions is mainly the result of spontaneous neurological recovery.[35, 36] The pathophysiological mechanisms that are known to underlie spontaneous neurological recovery are revival of penumbral tissue, alleviation of diaschisis, and perhaps some degree of synaptogenesis and neural rewiring within cortical networks adjacent to the brain lesion enabling the re-activation of damaged corticospinal pathways. This type of recovery typically leads to improved quality of movement.[37] Unfortunately, despite the presence of some training induced neuroplasticity in animal stroke models, there is very little evidence that in people with stroke physical training can promote restitution of sensorimotor functions beyond what can be predicted based on the proportional recovery rule.[37-39] In contrast, substitution of function is based on the optimal utilization of *spared* neural circuitry (e.g., ipsilesional premotor areas, contralesional (pre-) motor areas, brainstem), which can be facilitated by task-specific training to promote the learning of adjusted sensorimotor strategies. Usually, the acquisition of such strategies coincides with some loss of movement quality, as the same end result must be achieved with secondary neural pathways.[37] Thus, although training interventions do not seem to facilitate restitution of sensorimotor functions after stroke (ICF-impairment level), there is ample evidence that they *do* promote the re-acquisition of functional capacities (ICF-activities level), based on substitution of function and/or behavioural compensation.[39, 40]

As for the recovery of paretic leg motor control, it has been shown that this process occurs in a predictable manner for the majority of people after stroke.[33, 36] The recovery plateau of muscular coordination seems to be reached already in the very first weeks after stroke, as studies on the recovery patterns of leg muscle activation during gait did not show spatiotemporal changes beyond three weeks post stroke.[41, 42] Similarly, studies on standing balance recovery have provided hardly any proof of an increasing contribution of the paretic leg to standing balance in the post-acute phase of stroke.[27, 43] These observations were made in relatively severely affected subjects who were enrolled in inpatient rehabilitation programs. Although restitution of leg motor function may be better in less severely affected people, hardly any studies exist indicating that intensive rehabilitation leads to training-induced changes in muscle coordination patterns. The one study revealing training-induced changes in muscle coordination patterns in people after stroke achieved this result after high intensities of training that are not representative of regular rehabilitation.[44] Future research is needed to see whether this result can be replicated, which intensity of training is optimal, and whether this optimal dose is achievable in clinical practice. Until more evidence emerges, it does not seem feasible to actually train paretic leg motor control to improve the gait pattern after stroke. Instead, we should monitor the course of spontaneous neurological recovery and timely prescribe medical-technical interventions such as ankle-foot orthosis, functional electrical stimulation, focal spasmolysis, and ankle-foot surgery.[24]

Despite the disappointing results of physical training on paretic leg motor control, there is growing evidence that well targeted (dynamic) balance training is able to improve balance capacity after stroke. Several reviews (amongst others chapter 4 of this thesis) have shown that task-specific training, more specifically dynamically challenging balance and gait training, can improve balance capacity after stroke.[45, 46] Given the expected lack of improvement in paretic leg motor control, improved balance capacity can theoretically be explained by either improved trunk control ('core stability'), improved (i.e., more efficient) compensatory control executed by the non-paretic leg, and/or remitted learned non-use of residual balance capacity.

Improvement of trunk control usually occurs in the first month post stroke[47], primarily as a result of spontaneous neurological recovery. It follows the same time course as the recovery of arm and leg motor control.[47] However, initial paresis of the trunk muscles is typically less severe than paresis of the arm and leg muscles due the fact that the axial body muscles, in contrast to the extremity muscles, are *bilaterally* innervated. Trunk muscles receive input from the medial corticospinal tract that consists of descending fibers arising from cells in the motor area of both the contralateral and ipsilateral cerebral hemisphere.[48] Hence, the trunk has an excellent potential to compensate for lost function through the contralesional cerebral (i.e. non affected) hemisphere, which is probably the reason why initial paresis is usually mild and recovery of function usually good.[49] Another possibility is that the trunk muscles, more than the extremity muscles, are able to profit from intact *subcortical* (e.g., reticulospinal) innervation based on an important phylogenetic advantage. Indeed, from an evolutionary point of view, axial motor control is much older and strongly wired within subcortical neural networks, whereas extremity motor control, particularly of the wrist-hand and ankle-foot, has developed much later in human development and depends more heavily on cortical networks.[48] Yet, control of trunk movements through the reticulospinal tract may be associated with impaired movement quality, as motor control through this neural pathway is less refined than movements controlled by the cortex.[50] Nevertheless, from a neurophysiological point of view, both underlying mechanisms of recovery of trunk control can be considered forms of 'substitution of function', although clinically they may lead to near-normal control of the trunk muscles. This 'neurophysiological redundancy' of the axial body muscles may explain why physical training can promote functional recovery of the trunk and, thus, balance capacity when exercises are well targeted, even in the chronic phase after stroke.[51-53] Chapter 6 of this thesis substantiates this notion. In this chapter we found that trunk control improved in our participants who were in the chronic phase after stroke and showed relatively well recovered leg motor control (mean Fugl Meyer lower extremity score 74%). This improvement of trunk control was probably the result of targeted trunk exercises, which were part of the practice of fall techniques (see chapter 5).

Besides improved trunk control, it is well known that people after stroke rely heavily on their non-paretic leg for standing and walking[42, 43, 54-56] and that the non-paretic leg contributes to balance control up to 9 times more than the paretic leg in terms of corrective ankle torques.[57-59] Compensation through the non-paretic limb seems to be an effective sensorimotor strategy, as postural stability increases with increasing use of the non-paretic leg, even in severely affected stroke survivors.[58-60] As this compensation is (mainly) subserved by the intact contralesional hemisphere, task specific training of the non-paretic leg (for instance single-leg stance exercises) appears to have potential for improving balance capacity and regaining gait independence. This mechanism of functional recovery is clearly based on substitution of function, very much like persons with a lower limb amputation gradually master control of standing and walking with a lower limb prosthesis. Also in this population, evidence has been found for gradually more efficient motor control of the sound leg underlying the re-acquisition of balance and gait control.[61-63] Irrespective of the type of motor disorder, the motor control literature generally supports the notion that physical training promotes the (re-) learning of (adjusted) motor skills. This notion is particularly valid when undamaged neural and musculoskeletal systems can be used to acquire these skills.[64]

The above-mentioned compensation strategies after unilateral supratentorial stroke are specifically useful as long as balance and gait are relatively 'unperturbed'. This is reflected by the near-normal capacity of people with chronic stroke to sustain low intensity platform perturbations up to the level that a step has to be taken. Yet, when the perturbation intensity exceeds this so-called 'single stepping threshold', people with chronic stroke perform much worse than healthy controls, which is reflected by a much lower 'multiple stepping threshold'.[65] These difficulties in stepping responses to recover balance, in turn, lead to a greater risk of falling.[66] Hence, the loss of dynamic balance capacity after stroke particularly emerges in more demanding environments, when pro- and reactive balance control - and, thus, motor control of the paretic leg - become more important. Indeed, without sufficient control of the paretic leg, it is impossible to safely step with this leg or to use this leg as a safe support while stepping with the non-paretic leg. It is, therefore, important to focus on pro-and reactive stepping capacity with either leg. Fortunately, dynamic balance and gait training seem to have the potential of resulting in meaningful improvements for people after stroke.[31, 67-72] In fact, participants from our study in chapter 7 showed a mean increase of 3 to 4 degrees in the leg angle upon contact of the stepping foot after perturbation-based balance training. These gains in step quality were observed irrespective of whether participants preferred to use the non-paretic or the paretic leg for stepping in the forward and backward directions (which preference did not differ before and after training). Although the predictive value of this measure with regard to fall risk in people after stroke still needs to be established, it is known that in young healthy subjects a leg angle increase of just 1 degree results in a threefold greater odd of successfully recovering from a strong backward perturbation.

Given the poor trainability of paretic leg motor control (as discussed above), the question arises how improvements of step quality after stroke are achieved. Besides improving trunk control (as demonstrated by a modest increase in the Trunk Impairment Scale score after training) and improved use of the non-paretic leg, it might be that our training program promoted the use of residual motor capacity of the paretic leg by remitting so-called *learned non-use*. Reactive stepping is generally undertrained during in- and outpatient rehabilitation. In addition, this skill is hardly practiced in daily life, as people are relatively rarely exposed to perturbations of sufficiently high intensity for necessitating stepping reactions. Hence, targeted practice of reactive stepping by exposing people with stroke to challenging (but safe) circumstances may help them re-learn how to utilize residual motor control of the paretic leg. In addition to improvements in step quality, the participants in our perturbation-based balance training (chapter 7) also demonstrated gains in balance confidence (as measured with the Activity-Specific Balance Confidence Scale). This is an important finding, as improved balance capacity and confidence can lead to an increase in physical activity and, eventually, fewer falls.[73]

As described in the systems framework in the introduction of this thesis (figure 2), a variety of task-specific, individual and environmental factors influence balance and gait in daily life. Above, I have focused on the mechanisms of functional recovery and training from a sensorimotor perspective. It goes without saying that other factors, like post-stroke perceptual and cognitive deficits, are also important for functional recovery and need to be considered when designing and prescribing interventions to improve balance and gait.

Implications for rehabilitation of dynamic balance and gait after stroke

This thesis shows that interventions aimed at improving dynamic balance and gait may be beneficial for people in the chronic phase after stroke, although stronger evidence has yet to be provided by randomized controlled trials. Based on my research findings and clinical experiences with stroke rehabilitation in the Netherlands, I will share my vision on future rehabilitation of dynamic balance and gait for people after stroke.

Currently, a person who has suffered a stroke is initially admitted to a specialized acute care hospital unit (stroke unit) for diagnosis, treatment (e.g. thrombolysis), and the start of secondary prevention.[74-77] When a person suffers from persistent impairments that are prognosticated to affect long-term daily functioning, some form of (inpatient) rehabilitation is generally indicated. Treatment in an inpatient rehabilitation setting, either a specialized stroke rehabilitation center or a designated nursing home, primarily focuses on regaining independence of balance and gait and of basic activities of daily living (ADL) like dressing, bathing, grooming, feeding. When such independence is reached, generally after 6 to 12 weeks admission, people are typically discharged to a (pre-existent or adjusted) home situation. From this point, they often receive a similar period of outpatient multidisciplinary rehabilitation or community-based allied healthcare. This ambulatory care typically ceases when predefined individual goals are attained and no additional functional improvement by training is expected. Thereafter, people are monitored by a rehabilitation physician up to about one year after stroke to identify unmet mobility needs and to evaluate whether medical-technical interventions (e.g. an ankle-foot orthosis, focal spasmolysis, ankle-foot surgery) are indicated to further improve balance and gait capacities. A minority of people, particularly those with severe spasticity, receive prolonged allied healthcare, sometimes for several years, which often has a high 'maintenance character'. Interestingly, there is a growing body of evidence that this typical sequence within the focus of rehabilitation should be reconsidered. For instance, on the one hand, several studies have shown that the use of ankle-foot orthosis[78] and focal spasmolysis[79] to compensate for abnormal muscular activity and loss of gait stability and efficiency should commence already during the phase of inpatient rehabilitation while, on the other hand, training to improve balance and gait capacity may still be effective in the chronic phase after stroke. Moreover, many people lack the entrance to specialized functional surgery (e.g. ankle-foot rebalancing procedures) or high-tech training systems (e.g. C-mill[80], Grail[81], Zero-G[82]) to further increase their balance and gait capacity.

Generally, improving *dynamic* balance and gait after stroke deserves more attention in stroke rehabilitation. Moreover, the *timing* of this type of training should be tailored to the specific needs of individual patients. As stated above, during the first months after stroke, rehabilitation is typically focused on regaining balance and gait independence, but dynamic balance and gait training should already commence in this early phase to prepare people for the challenges they will face at home after discharge. Indeed, deficits in pro- and reactive balance control will leave them with an increased fall risk in the home situation, which explains the peak in fall incidence following discharge from inpatient rehabilitation.[73] Hence, some level of pro- and reactive balance control is necessary for a safe return home. Naturally, the exposure of people to new challenges at home will make them even more aware of specific deficits in their balance and gait capacities after discharge, which will enable them to define new goals. In this period of ambulatory care, dynamic balance and gait training should be intensified and even more targeted to patients' needs and interests. If these needs are not identified, balance and gait rehabilitation is terminated prematurely, which leaves people with tremendous challenges to overcome at home, but also to pick up leisure and working activities. If then secondary (often reactive) symptoms develop, such as fear, depression, and chronic fatigue, restored balance and gait capacities may even be lost due to lack of stimulation and promote learned nonuse.[73] This vicious circle of inactivity and subsequent loss of motor capacities should be avoided at all costs, as it inevitably predisposes to physical (e.g. cardiovascular) and mental (e.g. depression) morbidity and eventually premature death.

As mentioned above, balance and gait training is often terminated when people after stroke are just accustomed to function in the community. This is mostly based on the general belief that motor recovery plateaus in the first months after stroke,[32] closing a so-called 'window of opportunity', and that training in a later phase would therefore be ineffective. However, as argued above, the added value of early physical training for restoration of sensorimotor functions beyond the level of spontaneous neurological recovery is questionable (to say the least), whereas the value of training for the reacquisition of balance and gait capacities based on adjusted sensorimotor strategies is accumulating, even in chronic stroke. Indeed, previous studies have shown that functional improvements can occur when people in the chronic phase after stroke receive robot-assisted upper-limb rehabilitation[83] or executive function strategy training.[84] From chapters 4 and 7 of this thesis, we know that functional improvement in the chronic phase of stroke is also achievable by training dynamic balance and reactive stepping. The mechanisms underlying these 'late' training induced functional improvements are still elusive. For instance, is such improvement truly reached on top of the level achieved at the end of primary rehabilitation or is it perhaps based on the reacquisition of skills that were gradually lost due to inactivity after cessation of rehabilitation? And what is the importance of the use of new training modalities to achieve functional improvements in the chronic phase? Future research is needed to shed light on these issues. In the meantime, given the promising results of dynamic balance and gait training for people after stroke, I recommend to implement and critically evaluate such training in the various stages after stroke based on the individual needs and capacities of patients, with emphasis on the pre- and post-discharge primary rehabilitation phase as well as on the chronic phase (from 6 months) after stroke. In the chronic phase, community-dwelling people with stroke should have the opportunity to regularly train their dynamic balance and gait skills either at home, in community-based physiotherapy practices, or during booster sessions in specialized rehabilitation centers, depending on their motor and self-management skills.

But what should such a training program look like? First of all, these training programs should include dynamic trunk control exercises. The influence of trunk control on standing balance and concomitantly on gait independence supports the need to optimize trunk control during the various stages post stroke. Indeed, targeted trunk training has been shown to have a beneficial effect on standing balance capacity and gait after stroke.[85, 86] In chapter 6 of this thesis I too have been able to show that specific trunk exercises lead to improvements on clinical tests of trunk control and balance capacity. In addition, perturbation-based balance training as investigated in chapter 7 improved reactive stepping which coincided with improved trunk control, although this effect was not retained 6 weeks after training. Nevertheless, trunk control training seems an essential component of a rehabilitation program to improve dynamic balance and gait capacity after stroke.

Another important component of the rehabilitation program should be the training of reactive stepping and gait adaptability. Although the effects on fall outcome measures still need to be established, the results of such training on balance capacity and the ability to adjust one's steps during walking are very promising.[31, 72] Yet, the technical devices needed for these training programs, such as the Radboud Falls Simulator or the GRAIL[81], are not yet widely available. Alternatively, gait adaptability training may be delivered by applying physical step targets on the ground.[72] Perturbation training based on push or pulls by a physiotherapist has shown potential for improving dynamic balance and reactive stepping[68], but these modes of delivery may not be as challenging and intensive compared to, for instance, our training program on the Radboud Falls Simulator (as described in chapter 7). Fortunately, technical devices for training of reactive stepping and gait adaptability are gradually becoming more user-friendly and affordable. The C-mill[80], for instance, is becoming more widely available, also in some community-based physiotherapy practices. The FALLS program (chapters 5 and 6) is another option for such a setting, provided a sufficient number of patients within one practice are eligible for this type of training. Notably, the precursor of the FALLS program (the Nijmegen Falls Prevention Program) has already successfully been implemented in many community-based practices in the Netherlands and abroad, where local physiotherapists offer this program on a regular basis. To further increase training intensity and focus on reactive stepping and gait adaptations (such as those studied in chapter 3), training with technical devices may be added to this program. Moreover, to enhance the expertise of physiotherapists, we might need to centralize the community-based healthcare for people after stroke by setting up regional networks, comparable to ParkinsonNet, a successful low-cost healthcare innovation to optimize care for people with Parkinson's disease in the Netherlands.[87]

At all times, training should be sufficiently challenging. Motor learning is optimal when the difficulty of the task matches the skill level of the trainee.[88] In fact, the difficulty of the perturbation-based balance training program studied in chapter 7 of this thesis was aligned with the balance capacity of the participants before the training. But challenging training programs require a safe environment, which can be achieved using a harness or body weight support system. The use of new technical devices, such as virtual/augmented reality treadmills (for instance GRAIL[81] and C-Mill[80]) with the possibility of providing some degree of body weight support, can be an important intermediary step in the learning process. We should, therefore, offer patients the possibility of 'mixed interventions' that combine dynamic balance and gait training under safe circumstances in an outpatient rehabilitation clinic with home-based exercises, for instance based on motor imagery and action observation training. Indeed, the latter training modality appears to hold promise, particularly in the chronic phase after stroke[89, 90], as it activates similar cortical areas as those recruited during actual balance perturbations.[91]

To meet the changing needs of people after stroke, every stroke survivor with residual motor disabilities should see his/her rehabilitation physician well beyond the period of primary rehabilitation. International guidelines hardly provide recommendations on the preferred frequency of such outpatient control visits.[74-76] One exception is the UK stroke guideline (October 2016), which advises structured *annual* medical and social reviews from one year after stroke onwards.[77] In this way, interventions can be (re)offered to patients, if they meet their goals and if the potential for functional gain is good. Besides (booster) training sessions, there is an increasing arsenal of medical-technical interventions, such as functional electrical stimulation, advanced orthotics, targeted spasmolysis, and orthopaedic surgery that may potentially relieve complaints and improve function after stroke.

A future research perspective on dynamic balance and gait training after stroke

In addition to the suggestions for future research already mentioned above, I wish to end with a final research recommendation. The evidence presented and discussed in this thesis delivers a proof-of-principle for the efficacy of dynamic balance and gait training to improve stepping behavior and reactive balance in people with stroke. The question remains whether such improvements actually lower daily-life fall risk and prevent fall related complications in people after stroke. To this end, I recommend to conduct a randomized controlled trial of a multimodal training program, including dynamic trunk exercises as well as pro- and reactive balance and gait exercises as its main components. The primary outcome measure should include both fall rate and fall-related injury rate during a sufficiently long assessment period of at least one year. Preferably, secondary outcome measures assess the mechanisms underlying possible training effects. Ideally, these measures include the quality of pro- and reactive stepping, besides clinical scales of balance capacity and balance confidence. Based on these results, a cost-effectiveness analysis could be performed to estimate the medical and societal costs and savings. In the case of a positive cost-benefit ratio, this program should receive widespread (inter) national implementation in stroke rehabilitation services, comparable to the Nijmegen Falls Prevention Program for elderly persons.

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Chapter 9

Samenvatting in het Nederlands

Na een beroerte hebben veel mensen moeite met het handhaven van hun balans. Dit zorgt ervoor dat zij een grotere kans hebben om te vallen dan mensen die geen beroerte hebben gehad. De complicaties van een val, zoals het breken van een heup, en angst om te vallen, kunnen leiden tot lichamelijke inactiviteit, wat het leven van mensen die een beroerte hebben gehad sterk kan beïnvloeden. Dit is vooral van belang voor mensen die een hoog activiteitenniveau hebben en zich begeven in dynamische situaties, zoals buiten lopen op oneffen terrein of lopen in een drukke menigte.

Het doel van dit proefschrift is tweeledig. Ten eerste moet het leiden tot een beter begrip van balans en lopen in uitdagende en dynamische situaties, door te zoeken naar de oorzaken van de problemen die mensen na een eenzijdige beroerte hierbij ervaren. Daarnaast moet het inzicht geven in de effecten van dynamische balans- en looptraining na een beroerte. Hierbij ligt het accent op drie belangrijke, maar relatief onderbelichte componenten van dynamische balans en lopen: rompcontrole, het aanpassen van lopen aan de omgeving, en stapreacties na balansverstoringen.

In dit gedeelte vindt u een beknopte samenvatting van de bevindingen van dit proefschrift. Hoofdstuk 8 'Summary and general discussion' bestaat uit een uitgebreide samenvatting en discussie in het Engels.

Deel 1: Dynamische balans en lopen beter begrijpen

Hoofdstuk 2 bespreekt de bewegingen van het lichaam bij zijwaarts reiken door mensen die niet langer dan twaalf weken geleden een beroerte hebben gehad. Hierbij gaat het om een dynamische balanstaak die vraagt om goede rompcontrole. Zowel mensen na een beroerte als gezonde proefpersonen werden onderzocht. Zij voerden allen een gestandaardiseerde taak uit, waarbij hun gevraagd werd zittend zijwaarts te reiken naar de niet aangedane zijde. Mensen na een beroerte startten tijdens deze taak de beweging vanuit het bekken, gevolgd door de romp en het hoofd. Dit was tegengesteld aan het beweegpatroon van gezonde proefpersonen. Zij begonnen met het hoofd, waarna de romp en het bekken volgden. Daarnaast reikten mensen met een beroerte minder ver en bewogen zij langzamer. Deze resultaten laten zien dat de rompcontrole na een beroerte is aangedaan en dat dit het beweegpatroon beïnvloedt.

Hoofdstuk 3 richt zich op de mechanismen achter de problemen die mensen na een beroerte ondervinden bij het aanpassen van lopen aan de omgeving. Hiervoor werden de prestaties van mensen na een beroerte en gezonde controlepersonen vergeleken door middel van een taak waarin zij onverwachtse obstakels moesten ontwijken tijdens het lopen. Mensen na een beroerte lieten een opvallend lage successcore zien bij het ontwijken van obstakels, vooral als er sprake was van tijdsdruk. Ze toonden normale strategieën voor het ontwijken van het obstakel, maar voerden deze strategieën vertraagd uit met verlaagde spieractiviteit, kleinere afwijkingen van de gewrichtshoeken ten opzichte van het normale lopen en een kleinere horizontale afstand van de voet tot de obstakels.

Wij concludeerden dat zelfs bij mensen die mild aangedaan zijn door een beroerte, het aanpassingsvermogen tijdens het lopen is verminderd, wat het risico om te vallen vergroot.

Deel 2: training van dynamische balans en lopen

Om inzicht te krijgen in de effecten van oefentherapie op de balans van mensen in de chronische fase - meer dan 6 maanden na een beroerte - volgt een systematische beoordeling en analyse van de literatuur in **hoofdstuk 4**. Deze studie betreft een onderzoek naar gerandomiseerde en gecontroleerde studies van voldoende methodologische kwaliteit, in elektronische databases. Om te identificeren welk type training het meest effectief was, werden separate analyses verricht van balanstraining, looptraining, multisensore training en hoogintensieve aerobe training. Er werden 43 geschikte studies gevonden op basis van 369 zoekresultaten. De conclusie was dat het balansvermogen verbeterd kan worden door doelgerichte oefenprogramma's in de chronische fase na een beroerte en dat oefenprogramma's van het type balans- en looptraining het meest effectief zijn.

Hoofdstuk 5 laat de ontwikkeling en procesevaluatie van een valpreventie-oefenprogramma zien, specifiek gericht op mensen in de chronische fase na een beroerte (het FALLS-programma c.q. FALL prevention after Stroke). In de ontwikkeling van dit programma werd rekening gehouden met de specifieke behoeften en mogelijkheden van mensen die een beroerte hebben gehad. Het FALLS-programma werd getest bij twaalf mensen na een beroerte en een procesevaluatie werd uitgevoerd met patiënten, trainers, zorgprofessionals en managers. Mensen na een beroerte en zorgprofessionals beoordeelden het FALLS-programma als geschikt en uitvoerbaar.

Vervolgens geeft **hoofdstuk 6** een oriënterende studie weer naar het mogelijke effect van het FALLS-programma op een set van veel gebruikte klinische testen. Twaalf personen in de chronische fase na een beroerte namen deel aan een training van vijf weken met een totaal van tien sessies. Na de training lieten de deelnemers een betere balans en betere rompcontrole zien. De bevindingen van deze studie zijn veelbelovend voor mensen in de chronische fase na een beroerte en vragen om nader onderzoek in een gerandomiseerde en gecontroleerde studie met valfrequentie als primaire uitkomstmaat.

Een belangrijk probleem bij dynamische balanstaken voor mensen na een beroerte is het opvangen van een balansverstoring met een stap. **Hoofdstuk 7** vermeldt de resultaten van een studie die was opgezet om te zien of een trainingsprogramma de kwaliteit van dergelijke stapreacties kan verbeteren. Twintig personen na een beroerte ondergingen een trainingsprogramma met balansverstoringen op een beweegbaar platform in verschillende richtingen (twee trainingen van 45 minuten per week, gedurende vijf weken). Na de training lieten de deelnemers een verbetering van de kwaliteit van de stap zien na balansverstoringen in voor- en achterwaartse richting. Daarnaast lieten ze meer zijwaartse stappen zien na zijwaartse verstoringen. Deze effecten bleven zes weken na de training behouden. Klinische testen voor balans- en rompcontrole verbeterden direct na de training. Zes weken na de training was er nog steeds sprake van een verbeterde rompcontrole en hadden de deelnemers meer vertrouwen in hun balans. We concludeerden dat training op basis van balansverstoringen een goede methode is om zowel de kwaliteit van het stappen in voor-achterwaartse richting als het nemen van zijwaartse stappen in zijdelingse richting te verbeteren.

Appendices

Dankwoord | Acknowledgements

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Donders Graduate School for Cognitive Neuroscience

Dankwoord

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Lieve families, jullie zijn een warm Brabants thuis. Het is altijd fijn om in Waalwijk te zijn, zeker in het mooie nieuwe familiehuis. Ben en Ingrid, bedankt voor al jullie ondersteuning aan ons gezin (ik weet het, dat mag ik niet zeggen, want jullie doen het met veel plezier). Ook in Uden is het tegenwoordig een gezellige drukke bende bij ons thuis. En ja, dat is echt allemaal van ons. Ik geniet altijd enorm als we met z'n allen samen zijn. Manfred, dank je wel voor het laatste zetje op Kos. Willemijn, lief zusje, jij voelt als geen ander aan wat ik denk, voel en nodig heb. Wij kunnen geen twee weken zonder elkaar en ik ben blij dat onze mannen en kindjes dat precies zo hebben. Als ik het even niet meer weet, dan vraag ik het aan jou. Daarom ben ik zo blij dat jij vandaag, als paranimf, hier naast me staat.

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Curriculum Vitae

Hanneke van Duijnhoven was born in Waalwijk on February 3rd, 1984. After graduating from secondary school (Gymnasium, Dr. Mollercollege, Waalwijk) in 2002, she started to study medicine at the Radboud University Nijmegen. Hanneke performed her first research internship at the department of Rehabilitation of the Radboud University Medical Center in Nijmegen. Under supervision of dr. Vivian Weerdesteyn and prof. Sander Geurts, she studied obstacle avoidance in people in the chronic phase after stroke. Here, her love for balance and gait research and rehabilitation medicine was born. Hanneke graduated in 2009. Thereafter, she continued to work as a resident in rehabilitation medicine and subsequently in neurology. In 2010 she joined prof. Ann Ashburn and Dr. Geert Verheyden at the Stroke Association Rehabilitation Research Centre of the University of Southampton and studied lateral reaching in people after stroke. Later that year Hanneke started her residency in rehabilitation medicine at the sint Maartenskliniek (OOR Oost Nederland). During her residency she continued to do research on dynamic balance and gait after stroke. In 2015 she was awarded the 'Livit-trofee' for residents who have made an outstanding contribution to research in rehabilitation medicine. In the same year she won the best poster award at the Dutch Congress of Rehabilitation Medicine. Hanneke currently works as a rehabilitation physician at the Radboud University Medical Center and combines her clinical work with research and educational activities. Hanneke is married to Koen Kasper. They have two children, Lotte and Noud.

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Portfolio

Courses and workshops	Organizer	Year	ECTS
VRA cursus: Methode van revalidatie en bewegen, attitudevorming en communicatievaardigheden	RC Rijndam, Rotterdam	2010	1.5
VRA cursus: Klinische epidemiologie en statistiek	Department of Rehabilitation, Radboud University Medical Center	2011	1.0
VRA cursus: Houding en beweging	UMC Groningen	2011	1.5
VRA cursus: CVA	RC Blixembosch, Eindhoven	2012	0.5
Presentation Skills	Radboud in'to languages	2013	1.5
VRA cursus: sociale wetgeving en expertise	RC Reade, Amsterdam	2013	0.5
VRA cursus: neurofysiologie en gangbeeldanalyse	UMC Groningen	2013	0.5
VRA cursus: management	RC Rijndam, Rotterdam	2013	0.5
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	Radboud University Medical Center	2013	1.5
Introduction to data analysis	Erasmus Summer Programme	2013	1.5
Cursus bewegingsanalyse bij CVA patiënten	Roessingh Revalidatie, Enschede	2015	2.0
Cursus neuroanatomie	Radboud University Medical Center	2015	1.0
Cursus Balans Werk-Privé	RC Klimmendaal, Arnhem	2015	0.25
Writing week	Department of Rehabilitation, Radboud University Medical Center	2016	1.5
BROK herregistratie	Radboud University Medical Center	2017	0.15

Lectures and conferences	Location	Year	ECTS
Dutch congress on rehabilitation medicine	Ermelo, Noordwijkerhout, Rotterdam, Maastricht	2010, 2011, 2012, 2013, 2014, 2015, 2017	0.5
World congress on Neurorehabilitation	Melbourne, Istanbul, Philadelphia	2012, 2014, 2016	1.0
SMALLL jaarcongres	Antwerpen	2013	0.25
Symposium Kennis-netwerk CVA	Zeist	2014	0.5
Congress on Neurorehabilitation and Neural Repair	Maastricht	2015, 2017, 2019	0.5
Studiedag neuromotorische revalidatie	UZ Leuven	2017	0.5

Research data management according to the FAIR principles

General information about the data collection

Research projects within this thesis involve human subject data and written informed consent for collecting these data was obtained from all participants. Pre-existing data (chapter 2) were collected and stored by the Stroke Association Rehabilitation Research group at the University of Southampton. These data were used with permission. New data were collected and stored at the Radboud University Medical Center. Patient information was collected by a physician, only after informed consent was obtained. For the meta-analysis of chapter 4 we collaborated with dr. Janne Veerbeek and prof. Gert Kwakkel at the VU, Amsterdam. Data analysis and storage were performed at both locations.

FAIR principles

Findable: Data was stored on the server of the department of Rehabilitation at the Radboud University Medical Center. Paper CRF files were stored in the department's archive. Documentation to describe the datasets is provided on the department server. Data sets stored at the Radboud University Medical Center can be found on the department's server (Q:\Research\025 TBAS).

Accessible: It has not yet been possible to make the data available in a public repository. However, all data will be available on request by contacting the staff secretary of the department of Rehabilitation at the Radboud University Medical Center (secretariaatstaf.reval@radboudumc.nl).

Interoperable: Documentation was added to the data sets to make them interpretable. The documentation contains links to publications, references to the location of the data sets and description of the data sets. The data was stored in the following file formats: .xlsx (Microsoft Office Excel) and .mat (Matlab, Mathworks, USA). No existing data standards were used such as vocabularies, ontologies or thesauri.

Reusable: The data will be stored for at least 10 years and can therefore also be reused in this time period. There is no embargo on the accessibility of the data.

Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defenses please visit:
http://www.ru.nl/donders/graduate-school/phd/